DOI: 10.1002/ejoc.201100030

Enantiodivergent Transannular Rearrangement of 3-Isopropyl-1,4-benzodiazepine-2,5-dione by Memory of Chirality

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Keywords: Conformational equilibrium / Enantioselectivity / Lactam activation / Chirality / Rearrangement / Ring contraction

An unprecedented reactivity has been introduced to 3-isopropyl-1,4-benzodiazepine-2,5-dione thanks to *N*-Boc activation. Under basic conditions, a transannular rearrangement occurred by ring contraction to furnish a 3-aminoquinoline-2,4-dione with good to excellent enantiomeric purity. Depending on the nature of the base, either enantiomer can be obtained in a stereocontrolled manner. This enantiodivergent synthesis could be assigned to the conformational equilibrium of the starting material, which was studied with the help of DFT calculations.

Introduction

The development of stereoselective methods allowing the access to quaternary centers is a key synthetic goal and a major point of interest for organic chemists. Asymmetric construction of α,α-disubstituted amino acid derivatives have particularly been explored because of their biological properties and their scarce natural occurrence.[1] Conventional synthesis of such compounds requires chiral auxiliaries or chiral catalysts. However, during the last decade, the principle of Memory of Chirality (MOC) emerged as an elegant entry to these complex targets without the aid of any additional chiral sources.[2] This concept consists in the temporary storage of the stereochemical information at a different site in the intermediate. A significant example of this approach has been reported by Carlier and co-workers who exploited the ring flipping of benzodiazepin-2-ones.[3]

We recently published the unprecedented reactivity of 2,5-*dik*eto*p*iperazines (DKPs) bearing *tert*-butoxycarbonyl groups (Boc) on the nitrogen atoms, which display the role of electron-withdrawing activators (Figure 1). Such substituted lactams led to unusual transformations: enhancement of the opening ability of carbonyl lactam groups towards nucleophiles[4] or ring contraction by *t*ransannular *r*earrangement of *a*ctivated *l*actams (TRAL) under basic conditions.[5] In continuation of our efforts in this area, we hoped to extend this latter reaction to larger cyclic dipeptides. For this purpose, we chose 1,4-*b*en*zod*iazepine-2,5-diones (BZDs), a scaffold widely studied in its relation to medicinal chemistry.[6] In this paper, we describe the rearrangement of bis-Boc BZDs to 3-alkyl-3-aminoquinoline-2,4-diones in a stereocontrolled manner and in the absence of any external chiral source. To the best of our knowledge, there is no stereoselective pathway to these derivatives, and only one racemic preparation (by amination of halogenated intermediates) exists in the literature.[7] Nevertheless, quinoline-2,4-diones with a quaternary carbon center at C-3 possess anti-HIV[8] and 5-HT_6 serotonin receptor antagonistic activities.[9] This skeleton is also found in buchapine, a biologically active natural product with therapeutic potential.[10] In addition, 4-hydroxyquinolin-2-ones, analogous structures, exhibit a broad scope of pharmacological properties,[11] including antagonist behaviour at the glycine site of the *N*-methyl-D-aspartate receptor[12] and fatty acid synthase inhibition.[13]

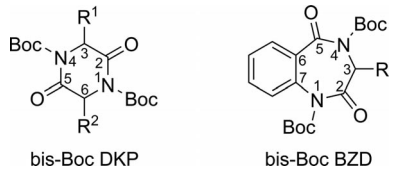

Figure 1. General structures of 1,4-bis(*tert*-butoxycarbonyl)piperazine-2,5-dione and 1,4-bis(*tert*-butoxycarbonyl)-1,4-benzodiazepine-2,5-dione.

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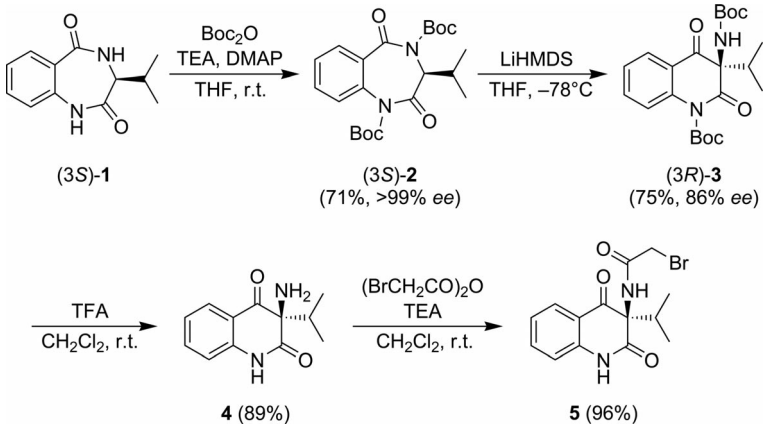
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100030.

Results and Discussion

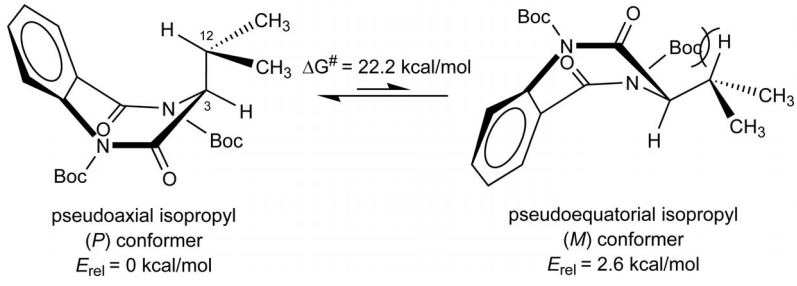
1,4-Benzodiazepine-2,5-diones were prepared according to a typical procedure by treatment of isatoic anhydride with an appropriate α-amino acid ester.[14] Investigations were conducted on compound (3*S*)-**1** with an isopropyl group at C-3. The insertion of Boc groups on the nitrogen atoms was carried out by using our previously reported protocol for the DKP series.[5a] The corresponding bis-Boc BZD (3*S*)-**2** was generated in good yield, and – according to chiral HPLC analyses – no racemisation occurred during this step (Scheme 1). Surprisingly, despite of our efforts, we were not able to isolate other diprotected BZDs, all attempts leading to N^1-Boc or *N*,*N*,*O*-tris-Boc products (see the Supporting Information).

With compound (3*S*)-**2** in hand, the dynamic equilibrium due to the presence of (*P*) and (*M*) conformational enantiomers was investigated by DFT/PCM calculations at the B3LYP/SDD level of theory.[15,16] This study revealed that the conformer with the isopropyl group in pseudoaxial position is the most stable one, probably because of less steric hindrance between the isopropyl and the N^4-Boc groups (Scheme 2). In addition, the barrier height for the conversion of the (*P*) to the (*M*) conformer was calculated to be 22.2 kcal/mol. These results are in agreement with a previous report, which mentions the importance of the size of the N^1-substituent for the inversion barrier.[17] Some insight into the conformation in solution can be gleaned from a careful examination of the ^{1}H NMR spectrum. At room temperature, only one set of peaks was observed in $CDCl_3$. The coupling constant $^3J_{3\text{-H},12\text{-H}}$ was measured to be 11.1 Hz, a large value consistent with a *trans* relationship. In addition the 12-H chemical shift was recorded at δ = 1.04 ppm, an upfield shift meaning that this proton is located in the cone-shaped shielding zone due to the aromatic ring. Furthermore, nOe experiments clearly confirmed that this latter hydrogen atom is close to those belonging to the aromatic moiety. All these observations suggest that, at room temperature and in solution, bis-Boc BZD **2** adopts a conformation in which the isopropyl group is oriented in pseudoaxial position.

As expected, in the presence of lithium hexamethyldisilazide (LiHMDS), we observed a ring contraction of BZD (3*S*)-**2**, leading to 3-aminoquinoline-2,4-dione (3*R*)-**3** in good yield and with excellent enantioselectivity (Scheme 1). Removal of the Boc groups was easily achieved by using trifluoroacetic acid, and subsequent treatment with bromoacetic anhydride afforded derivative **5**. The configuration of the quaternary stereogenic carbon center was thus unambiguously determined by X-ray diffraction crystal analysis of the major isomer **5**, enantioenriched by recrystallisation (Figure 2).[18] At this stage, it is interesting to note that Juaristi et al. have already reported 3-alkylation of 1,4-benzodiazepine-2,5-diones bearing alkyl chains on the nitrogen atoms in the presence of a strong base, but did not observe any rearrangement.[19]



Scheme 1. Stereocontrolled transannular rearrangement of an activated BZD derived from L-valine.



Scheme 2. Conformational equilibrium of bis-Boc BZD (3*S*)-**2**. E_{rel} = relative energy with respect to the most stable conformation.

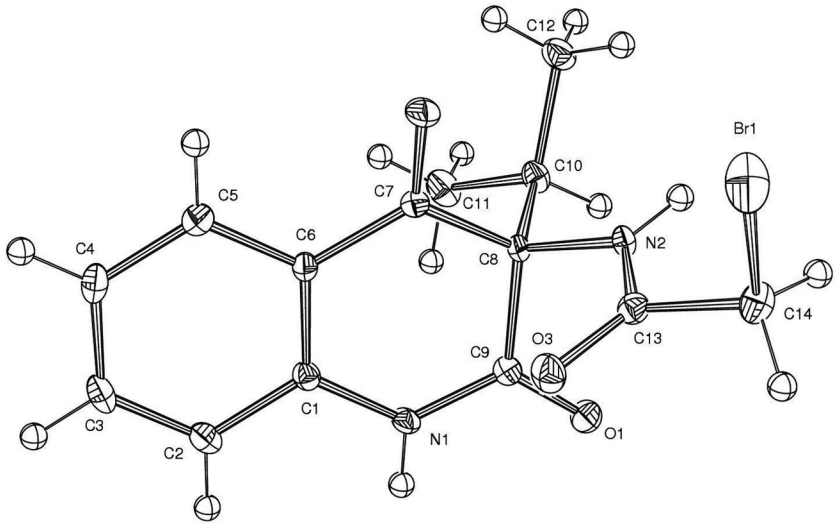
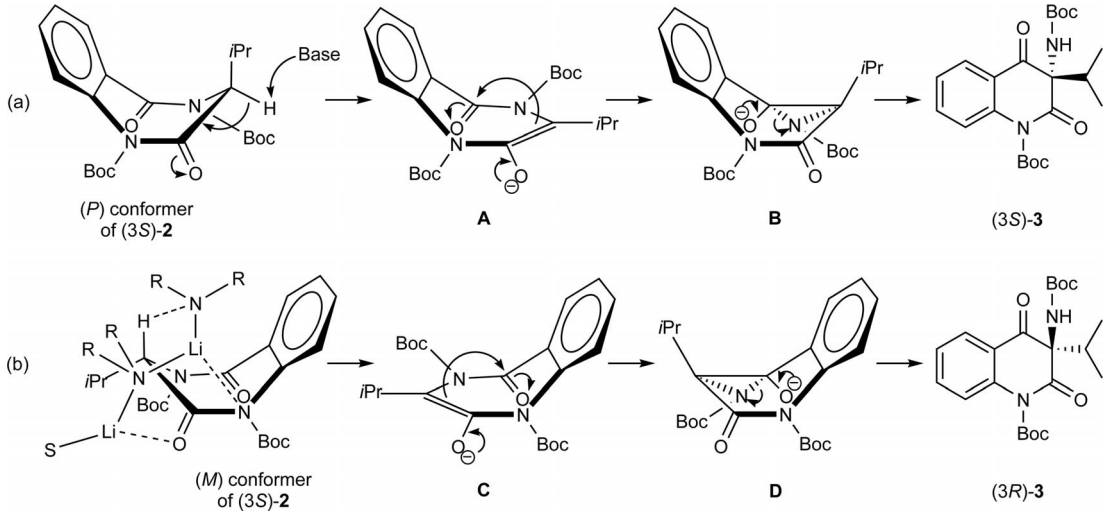


Figure 2. ORTEP representation of (3*R*)-**5**.

We propose for this unusual transformation a mechanism very similar to the TRAL in the DKP series.[5a,5c] Under basic conditions, the resulting enolate attacks the activated lactam carbonyl group to promote an oxy anion with an aziridine moiety, which opens to furnish the desired product (Scheme 3). This can be related to the Chan reaction,[20] a base-induced rearrangement of an acyloxyacetate to a 2-hydroxy-3-oxo ester, and the N → C acyl migration of an acyclic imide,[21] two rare tools used in the total syntheses of aplasmomycin,[22] boromycin,[23] rapamycin,[24] diazonamide A[25] and taxol.[26]

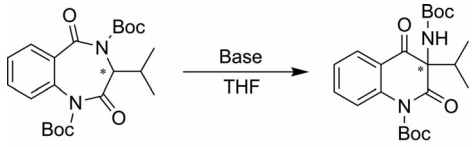
In order to explore this original reactivity, bis-Boc BZD **2** was subjected to other bases (Table 1). Attempts carried out with stronger lithiated bases, such as lithium diisopropylamide (LDA, Entry 1) or *n*-butyllithium (*n*BuLi, Entry 2), were unsuccessful and led to complex mixtures of compounds difficult to analyse. KHMDS provided the desired quinoline-2,5-dione in excellent yield and with good enantiomeric ratio (Entry 5). The use of NaH gave worse results (Entry 6), and potassium *tert*-butoxide appeared as a moderate reagent (Entry 7), whereas a significant improvement was obtained with 4-(dimethylamino)pyridine (DMAP, Entry 8). It is noteworthy that good enantiomeric excess can be achieved with these three bases, although the temperature was relatively high for this type of reaction. A similar observation has previously been made in a cyclization process by MOC for the synthesis of quaternary amino acids.[27]

However, the most exciting finding is undoubtedly the fact that starting from an enantiopure benzodiazepine, it is possible to obtain stereospecifically both enantiomers of the quinoline by changing the nature of the base. With LiHMDS, the rearrangement proceeds preferentially with inversion of configuration, whereas retention of configuration is observed with other bases (for example: Entry 3 vs. Entry 5). A plausible explanation could be found in the



Scheme 3. Possible mechanism to explain the observed stereoselectivity of the reaction. Base: KHMDS, NaH, *t*BuOK, DMAP; R = $SiMe_3$; S = solvent.

Table 1. Effects of base on the stereochemical course of the rearrangement of **2**.



2 **3**

Entry	**2**	Base	*T* [°C]	**3**, yield [%][a,b]	Enantiomeric ratio[c]
1	(3*S*)	LDA	–78	–, 0	–
2	(3*S*)	*n*BuLi	–78	–, 0	–
3	(3*S*)	LiHMDS	–78	(3*R*), 75	93:7
4	(3*R*)	LiHMDS	–78	(3*S*), 76	7:93
5	(3*S*)	KHMDS	–78	(3*S*), 87	19:81
6	(3*S*)	NaH	0	(3*S*), 5	17:83
7	(3*S*)	*t*BuOK	0	(3*S*), 52	28:72
8	(3*R*)	DMAP	20	(3*R*), 84	86:14

[a] The absolute configuration of the major isomer is indicated. [b] Yield of product isolated by flash chromatography. [c] Ratio (*R*)/(*S*) was determined by HPLC on a chiral phase.

conformational equilibrium of the starting material. Carlier and co-workers described the alkylation of 1,4-benzodiazepine-2,5-dione derived from proline in the absence of permanently chiral elements in the system. The authors assumed that this phenomenon is due to MOC.[28] To give a hypothetical mechanism in our case, we propose that non-lithiated bases remove the acidic hydrogen atom from the most stable conformer [(*P*) conformer] as illustrated in Scheme 3a. The only stereogenic carbon center is destroyed, but the conformation of the molecule induces the formation of the aziridine on the less bulky half-space to generate oxy anion **B**. Finally, the opening of this aziridine generates (3*S*)-**3**. In contrast, a different behaviour is noticed with LiHMDS, since **3** is obtained with inversion of configuration in comparison to the starting material (Entries 3 and 4). This means that the deprotonation occurred on the (*M*) conformer. Such phenomenon has already been highlighted by Kawabata et al. who referred to chelation effects.[29] In addition, LiHMDS is well known to form a dimer in THF,[30] which has to be opened for effective deprotonation.[31] We can envisage that this transition structure is more favoured in the case of the (*M*) conformer due to a suitable approach by chelation (Scheme 3b).

Conclusions

We have described the extension of the TRAL reaction to a seven-membered ring, 3-isopropyl-1,4-benzodiazepine-2,5-dione, leading to the first enantioselective synthesis of 3-aminoquinoline-2,4-dione, a valuable scaffold with pharmacological potential. The stereochemistry of the rearrangement depends on the base used. Studies are currently directed to obtain further insight into this enantiodivergent synthesis. We also envision to expand the scope of the TRAL to activated lactams included in macrocycles.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data for all compounds and details on the DFT calculations for (3*S*)-**2**.

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Received: January 10, 2011
Published Online: February 21, 2011

