Heterocycles

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[3,3]-Sigmatropic Rearrangement/Allylboration/Cyclization Sequence: Enantioenriched Seven-Membered-Ring Carbamates and Ring Contraction to Pyrrolidines

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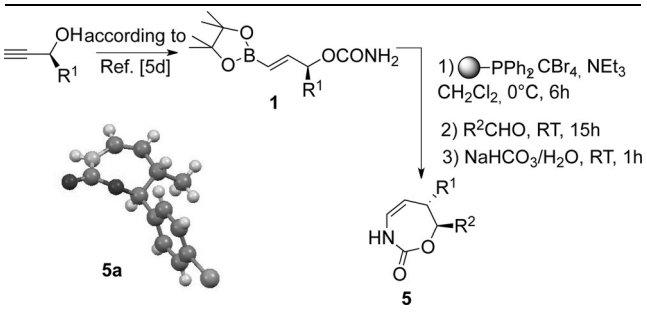
Abstract: *The combination of in situ generated α-isocyanato allylboronic esters and aldehydes afforded seven-membered-ring enecarbamates with high levels of diastereo- and enantiocontrol. They were easily converted into diversely substituted 1,3-oxazepan-2-ones. An unprecedented rearrangement of 5-acetoxy-7-aryl or styryl derivatives led to tetrasubstituted pyrrolidines. A computational study provides evidence on the feasibility of the proposed mechanism of this unusual ring contraction.*

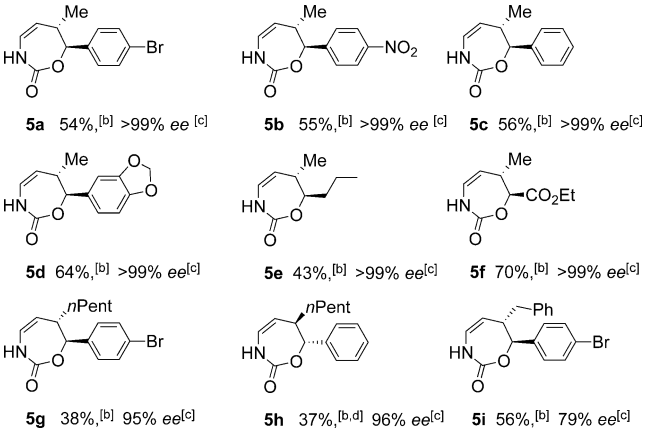
Nitrogen heterocycles are widespread in a plethora of molecules of interest, either in materials science, electronics, optics, or biology.[1] Among these, seven-membered-ring carbamates are relatively under-represented despite their interesting biological activities.[2] Several approaches are available for their synthesis, and the most common ones are based on intramolecular cyclization of 1,4-aminoalcohols or derivatives.[3] Others are restricted to isolated examples or very particular structures.[4] Our interest in the use of boronic esters in cascade reactions[5] led us to consider their utility for the synthesis of enantioenriched 4,5-dihydro-1,3-oxazepin-2-ones. These versatile intermediates led, through an unprecedented ring contraction reaction, to tetrasubstituted pyrrolidines, another family of major biological significance.

Access to the key carbamates **1** was first achieved from optically active 1-alkyn-3-ols.[6,7] Dehydration with phosphine and carbon tetrabromide in the presence of triethylamine,[5d] followed by direct addition of aldehydes to the crude reaction mixture, and then aqueous $NaHCO_3$ 15 hours later, afforded the cyclic ene carbamates **5** in good to moderate yields (three-step process; Table 1). The structure of **5** was assigned on the basis of NMR data and X-ray crystallographic analysis of **5a**.[8]

The following mechanism can be proposed. After dehydration of **1**, the resulting allylcyanate **2** undergoes a [3,3]-sigmatropic rearrangement which affords the α-isocyanato allylboronate **3** (Scheme 1).[5d,9,10] A chairlike transition state

Table 1: Synthesis of the enecarbamates **5**.[a]





[a] The reactions were carried out by addition of a solution of CBr_4 (0.56 mmol, 2.8 equiv) in CH_2Cl_2 (0.5 mL) to a mixture of **1** (0.2 mmol), polymer-supported phosphine (2.5 equiv), and Et_3N (0.4 mmol, 2 equiv) in dry CH_2Cl_2 (2 mL). The aldehyde (0.24 mmol, 1.2 equiv) was added after 6 h at 0°C. The mixture was maintained at RT for 15 h before quenching with aqueous $NaHCO_3$. [b] Yield of product isolated after silica gel chromatography. [c] Determined by GC for the starting 1-alkyn-3-ols [(*S*) R^1 = Me, *ee* > 99%, (*S*) R^1 = *n*-Pent, *ee* = 96%, (*R*) R^1 = *n*-Pent, *ee* = 96%, (*S*) $R^1 = CH_2Ph$, *ee* = 86%] and HPLC for **5** using a chiral stationary phase. [d] *R* enantiomer.

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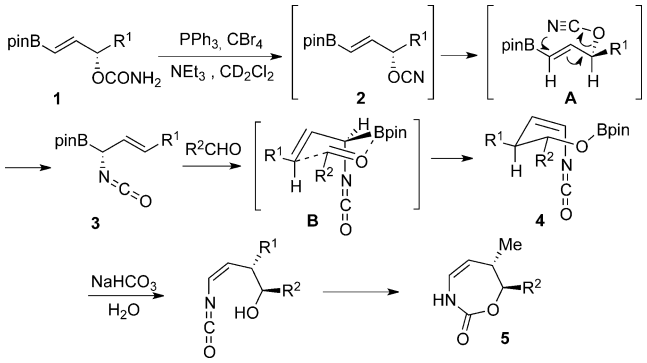
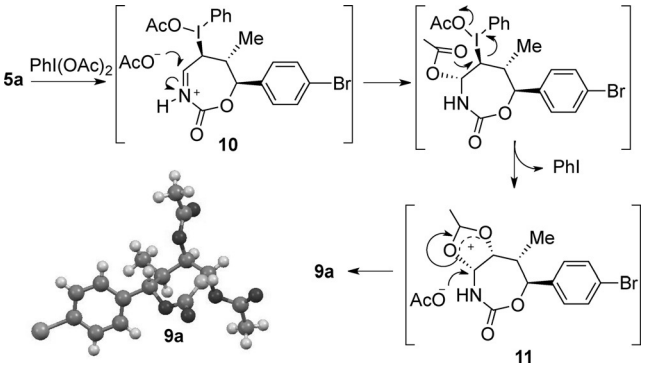


Scheme 1. Proposed mechanism for **5**→**1**. pin = pinacol.

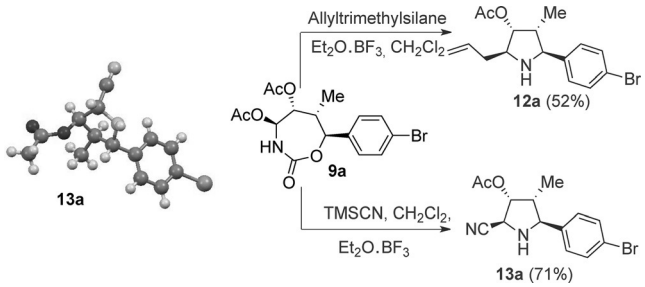


Scheme 3. Proposed mechanism for the formation of **9a**. THF = tetrahydrofuran.

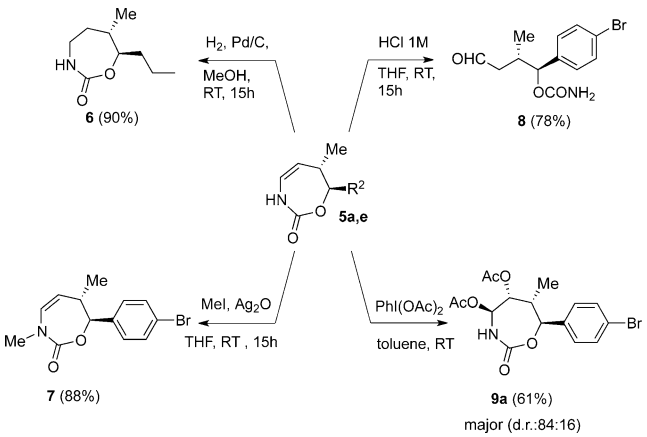
in which 1,3-diaxial interactions are minimized (intermediate **A**) explains the *E* geometry of the new double bond. Concerning the allylation step, its stereochemical course can be rationalized by the favored transition-state **B**. The NCO group adopts a pseudoaxial position because of the presence of a polar α-substituent and the relatively bulky pinacol moiety.[11] Finally, an intramolecular cyclization occurs after cleavage of the O–B bond (see the Supporting Information for a detailed ^{1}H NMR study). No erosion of the stereochemical integrity of the starting alkynol was observed for **5a–h** (Table 1), thus demonstrating that the [3,3]-sigmatropic rearrangement occurred with complete 1,3-chirality transfer. In the case of **5i**, partial loss of chiral information could result from the participation of a cationic phenonium intermediate which is trapped by S_N2' addition of the cyanate anion.[12–14]

Enecarbamates have been the center of intense interest over the past few years[15,16] and led us to explore the reactivity of **5** (Scheme 2). Hydrogenation with H_2 in the presence of Pd/C and methylation mediated by silver oxide afforded **6** (90%) and **7** (95%), respectively. Treatment with 1 M HCl in THF caused ring opening to provide the aldehyde **8**, and vicinal dioxygenation using $PhI(OAc)_2$ occurred in high yield to afford **9a** as the major isomer.[8,16g]

This selectivity is consistent with the mechanism proposed in Scheme 3. The N-acyliminium intermediate **10** underwent addition of the acetate anion anti to the bulky α-iodo substituent. Nucleophilic displacement of PhI, assisted by the neighboring OAc substituent, led to the oxonium ion **11** which then afforded **9a**. α-Acetoxycarbamates are prone to undergoing Lewis acid catalyzed reactions with diverse nucleophiles.[17] The compound **9a** indeed reacted with either allyltrimethylsilane or TMSCN in the presence of $Et_2O.BF_3$ (Scheme 4). Surprisingly, instead of the expected seven-membered ring, the pyrrolidines **12a** and **13a**, respectively, were produced as single isomers.[8] These compounds belong to the 3-hydroxypyrrolidine family, which is found in a wide range of natural products and drug intermediates.[18]



Scheme 4. Synthesis of the pyrrolidines **12a** and **13a** from **9a**. TMS = trimethylsilyl.

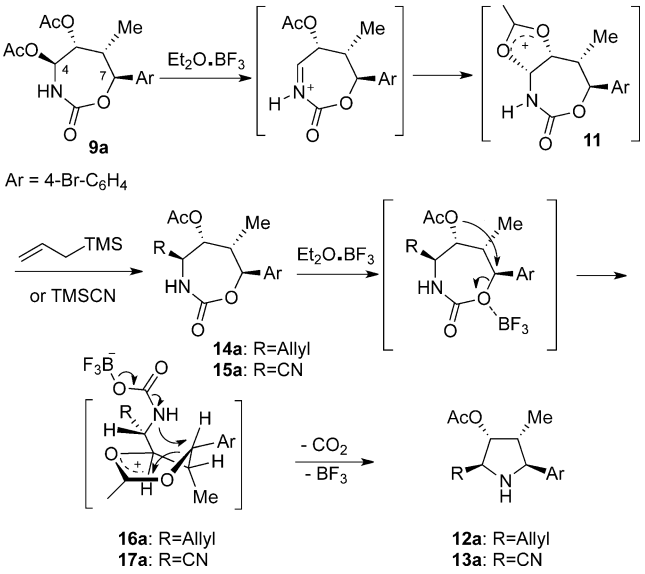


Scheme 2. Functionalization of **5**.

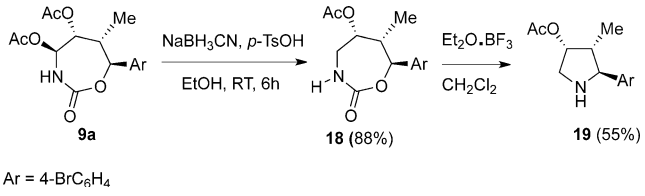
We hypothesized that either the 1,3-oxazepan-2-one **14a** or **15a** was initially produced following a classical reaction pathway (Scheme 5), with the relative configuration at C4 directed by the formation of an oxonium intermediate **11** (Scheme 3). After the coordination of the oxygen atom of the carbamate to boron, an intramolecular displacement by the acetate group afforded either **16a** or **17a**, which, in turn, was subjected to the attack of the internal nitrogen atom with concomitant release of CO_2.

A supplementary experiment confirmed the hypothesis of a 1,3-oxazepan-2-one intermediate. Reduction of **9a** with $NaBH_3CN$ gave **18** in 88% yield with no pyrrolidine formation. Further treatment with $Et_2O.BF_3$ led to ring contraction to furnish **19** (Scheme 6).

To check the plausibility of this ring contraction, we calculated the reaction profile associated with the **15**→**13** transformation. We used M06-2X[19] (including solvent



Scheme 5. Proposed mechanism for the formation of **12a** and **13a**.



Scheme 6. Synthesis of **19** from **9a**. Ts = 4-toluenesulfonyl.

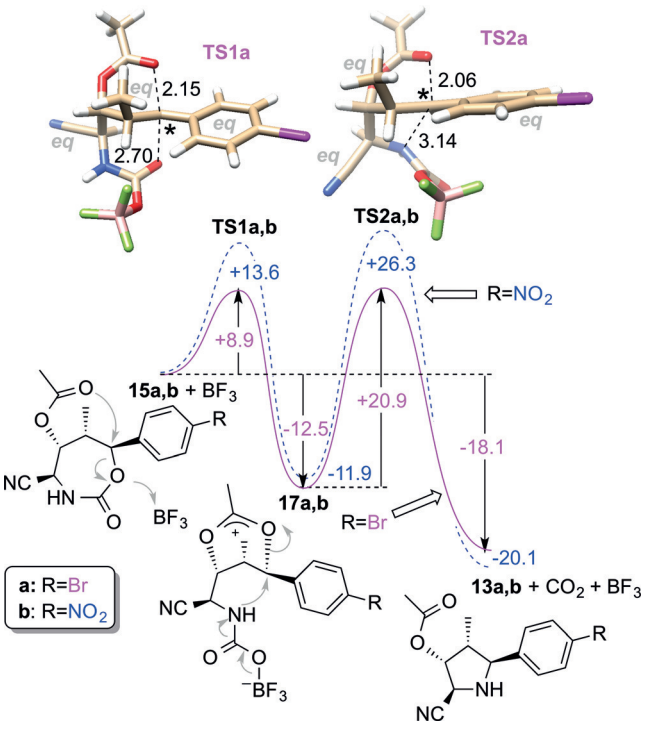


Figure 1. Reaction profile and stationary points associated with the **15a,b**→**13a,b** transformations. All the calculations were performed at the M06-2X(PCM = CH_2Cl_2)/6–31 + G*//B3LYP/6–31G* level of theory. Relative standard free energies and bond distances are given in kcal mol^{-1} and Å, respectively.

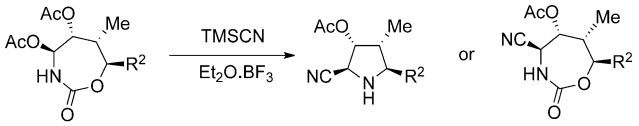
effects[20]) and B3LYP[21] hybrid DFT functionals for single-point calculations and geometry optimizations, respectively. The reported results correspond to the M06-2X(PCM = CH_2Cl_2)/6-31 + G*//B3LYP/6–31G* level of theory as implemented in the Gaussian 09 suite of programs.[22] According to these results (Figure 1), the intermediate **15a** coordinates to BF_3, thus generating a more polar species which gives the zwitterionic intermediate **17a** (6-*exo-tet* process). The NH moiety then acts as a nucleophile to form the pyrrolidine **13a** by a second intramolecular 5-*exo-tet* cyclization, with concomitant loss of OAc, release of CO_2, and recovery of BF_3. This latter event provides a favorable entropic balance, which is compatible with the exergonocity computed for the **15a**→**13a** transformation.

Two additional factors contribute to the efficient conversion of **15a** into **13a**: first, the benzylic character of the carbon atom on which the two consecutive nucleophilic substitutions take place; second, the stereogenic centers bearing the CN, Me, and aryl groups in **TS1a** and **TS2a** possess an adequate configuration to occupy equatorial positions, and thus results in less congested saddle points (Figure 1). Formally, both consecutive nucleophilic substitutions can be envisaged as S_N2 reactions via the saddle points **TS1a** and **TS2a**. However, in both transition structures, the bond orders between the C_{ipso} group and the nucleophiles and the leaving groups are quite low. Thus the $C_{ipso}H$ groups in **TS1** and **TS2** have a significant cationic character. The computed NBO charges for $C_{ipso}H$ in **TS1a** and **TS2a** are + 0.45 e and + 0.44 e, respectively. Accordingly, a π-electron withdrawing group at the 4-position of the aryl group (R^2) should result in larger activation energies. In effect, the transition structures **TS1b** and **TS2b** are significantly destabilized with respect to their respective bromo congeners and the corresponding activation energies are 4.7 kcal mol^{-1} and 5.4 kcal mol^{-1} higher than those associated with **TS1a** and **TS2a**, respectively. In terms of relative rates, the theoretical kinetic ratio at 298 K is *rate*(NO_2):*rate*(Br) ≈ 10^{-6}. This much lower reactivity was confirmed experimentally, as no pyrrolidine formation was observed from **9b** (see Table 2).

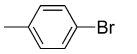
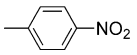
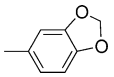
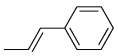
To better define the scope of the ring contraction process, several additional 4,5-diacetoxy-1,3-oxazepanones (**9**) were reacted with TMSCN in the presence of $Et_2O.BF_3$ (Table 2). Depending upon the R^2 substituent, and, in agreement with the previous theoretical study, the pyrrolidines **13c**, **13d**, and **13j** were obtained in good yields while seven-membered rings were only produced from **9b** and **9e**.

In conclusion, we have developed an efficient [3,3]-sigmatropic rearrangement/allylboration/cyclization sequence which gives access to cyclic enecarbamates. These versatile intermediates can be further engaged in a series of functional-group modifications. An unprecedented ring contraction reaction was demonstrated to be a promising strategy for the enantiocontrolled synthesis of tetrasubstituted pyrrolidines. The scope and limitations of this process were determined and computational evidence fully supports the

Table 2: Reactivity of 4,5-diacetoxy-1,3-oxazepan-2-ones **9**.



9 **13** **15**

Entry	**9**	R^2	Yield [%][a] **13**	**15**
1	**9a**		71	–
2	**9b**		–	70
3	**9c**		59	–
4	**9d**		87	–
5	**9e**		–	71
6	**9j**		73	–

[a] Yield of product after purification by silica gel chromatography.

proposed mechanistic hypothesis. Subsequent synthetic applications are currently being explored in our laboratories.

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