JOC Article

Theoretical Study of the Mechanism of the Formation of 3-Unsubstituted 4,4-Disubstituted β-Lactams by Silver-Induced Ring Expansion of Alkoxycyclopropylamines: A New Synthetic Route to 4-Alkoxycarbonyl-4-alkyl-2-azetidinones

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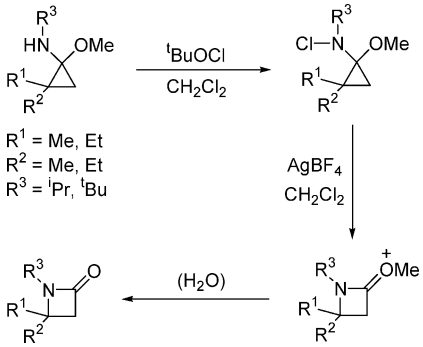
The mechanisms of formation of 4,4-dialkyl- and 4-alkoxycarbonyl-4-alkyl-2-azetidinones by silver-induced ring expansion of the corresponding 2,2-disubstituted *N*-chloro-1-hydroxycyclopropylamines were theoretically investigated by means of the B3LYP method and the PCM solvation model. The obtained results indicate that these reactions are facile two-step regioselective processes proceeding through a short-life nitrenium intermediate. The theoretical results thus predict that this synthetic strategy, which has already been used to obtain 4,4-dialkyl-2-azetidinones, could also be a new route to efficiently obtain in a regio- and stereoselective way 4-alkoxycarbonyl-4-alkyl-2-azetidinones, which are precursors of conformationally constrained amino acids.

Introduction

The introduction of two substituents at the C4 of the β-lactam ring is important because it leads to compounds stable to both chemical and enzymatic hydrolysis, although still maintaining good antibacterial activity.[1] 4,4-Disubstituted β-lactams are also powerful small building blocks for natural product synthesis.[2] 4,4-Dialkyl β-lactams have been synthesized by regiospecific electrophile- and silver-induced ring expansion of the corresponding 2,2-disubstituted 1-methoxycyclopropylamines (see Scheme 1) following a synthetic strategy first designed by Wasserman, who proposed that this ring enlargement sequence could take place through a nitrenium ion species or by a concerted process.[3] Almost all β-lactams were obtained in good to excellent yields (75−99%).[4]

The mechanism of this process has been interpreted by *N*-chlorination of 1-methoxycyclopropylamines to give the corresponding *N*-chlorocyclopropylamines, and silver-assisted rearrangement by which the electron pair of the methoxy oxygen atom is pushing the electrons toward ring opening and expulsion of chloride (push−pull mechanism). The resulting oxonium species undergoes further hydrolytic cleavage during workup. The regioselectivity of this process arises from the better migratory aptitude of the *gem*-disubstituted ring carbon to neutralize the intermediate pseudonitrenium species.

SCHEME 1. Synthesis of 4,4-Dialkyl-2-azetidinones from 2,2-Dialkyl-1-methoxycyclopropylamines



More recently, the first synthesis of 3-unsubstituted 4-alkoxycarbonyl-4-alkyl-2-azetidinone derivatives has been reported.[5] The importance of these compounds as structural units for incorporating conformational restraints in peptides, and as synthetic intermediates in the preparation of secondary structure mimetics, has increased in recent years.[6] This synthesis, which presents only a moderate enantioselectivity, has been carried out through the intramolecular alkylation of different *N*-benzyl-*N*-chloroacetyl-derived amino acids, involving the formation of the C3−C4 bond of the β-lactam ring as the key step (see Scheme 2).

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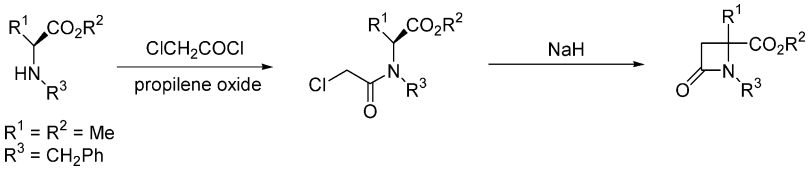
SCHEME 2. Synthesis of 4-Alkoxycarbonyl-4-alkyl-2-azetidinones from Amino Acids



Trying to learn about the mechanism of the silver-induced ring expansion of cyclopropylamines already exploited experimentally, in this paper we present a theoretical study of the silver-assisted ring expansion of *N*-chloro-*N*-methyl-2,2-dimethyl-1-hydroxycyclopropylamine (**1**) to yield *N*-methyl-4,4-dimethyl-2-azetidinone. We also report the results obtained in a computational study of the silver-assisted ring expansion of *N*-chloro-*N*-methyl-1-hydroxy-2-methoxycarbonyl-2-methylcyclopropylamine to yield *N*-methyl-4-methoxycarbonyl-4-methyl-2-azetidinone, which are important as precursors of conformationally constrained amino acids and generators of molecular diversity. This process could be a new stereoselective synthetic route to these molecules.

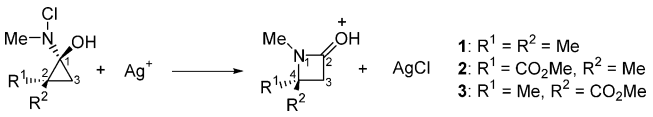
Computational Details

Full optimizations were performed with the B3LYP DFT method,[7] using the relativistic effective core pseudopotential LANL2DZ[8] added to one set of *f* polarization functions (ζ_f = 0.473) for Ag and the 6-31+G(d) basis set for the remaining atoms employing the Gaussian 98 series of programs.[9] This theory level has been shown to be adequate[10] to study reactions between organic molecules and Ag^+. The nature of the stationary points was further checked and zero point vibrational energies (ZPVEs) were evaluated by analytical computations of harmonic vibrational frequencies at the same theory level. Intrinsic reaction coordinate (IRC) calculations were also carried out to check the connection between the transition states (TSs) and the minimum energy structures, using the Gonzalez and Schlegel method[11] implemented in Gaussian 98. ΔG values were also calculated within the ideal gas, rigid rotor, and harmonic oscillator approximations.[12] A pressure of 1 atm and a temperature of 298.15 K were assumed in the calculations.

To take into account condensed-phase effects we used a self-consistent-reaction-field (SCRF) model proposed for quantum chemical computations on solvated molecules.[13−15] The solvent is represented by a dielectric continuum characterized by its relative static dielectric permittivity ϵ_o. The solute, which is placed in a cavity created in the continuum after spending some cavitation energy, polarizes the continuum, which in turn creates an electric field inside the cavity. This interaction can be taken into account using quantum chemical methods by minimizing the electronic energy of the solute plus the Gibbs energy change corresponding to the solvation process.[16] Addition of $\Delta G_{gas-phase}$ to the solvation Gibbs energy, evaluated neglecting the change in the relative value of the thermal corrections when going from a vacuum to the solution, gives $\Delta G_{solution}$. Within the different approaches which can be followed to calculate the electrostatic potential created by the polarized continuum in the cavity, we have employed the polarizable continuum model (PCM)[17] with Bondi's atomic radii. The solvation Gibbs energies $\Delta G_{solvation}$ along the reaction coordinate were evaluated from single-point PCM calculations on the gas-phase optimized geometries at the same theory level. A relative permittivity of 8.93 was employed to simulate dichloromethane as solvent used in the experimental work.

B3LYP charge densities were analyzed by means of the Theory of Atoms in Molecules developed by Bader[18] and with the AIMPAC package.[19]

SCHEME 3. Reactions Studied in the Present Work



Results and Discussion

The theoretical results obtained for the three reactions studied in the present work (see Scheme 3) are displayed in Table 1 and in Figures 1−4.

Absolute electronic energies, ZPVEs, and Cartesian coordinates of optimized geometries of all the critical structures located along the reaction coordinates are available as Supporting Information. Unless otherwise

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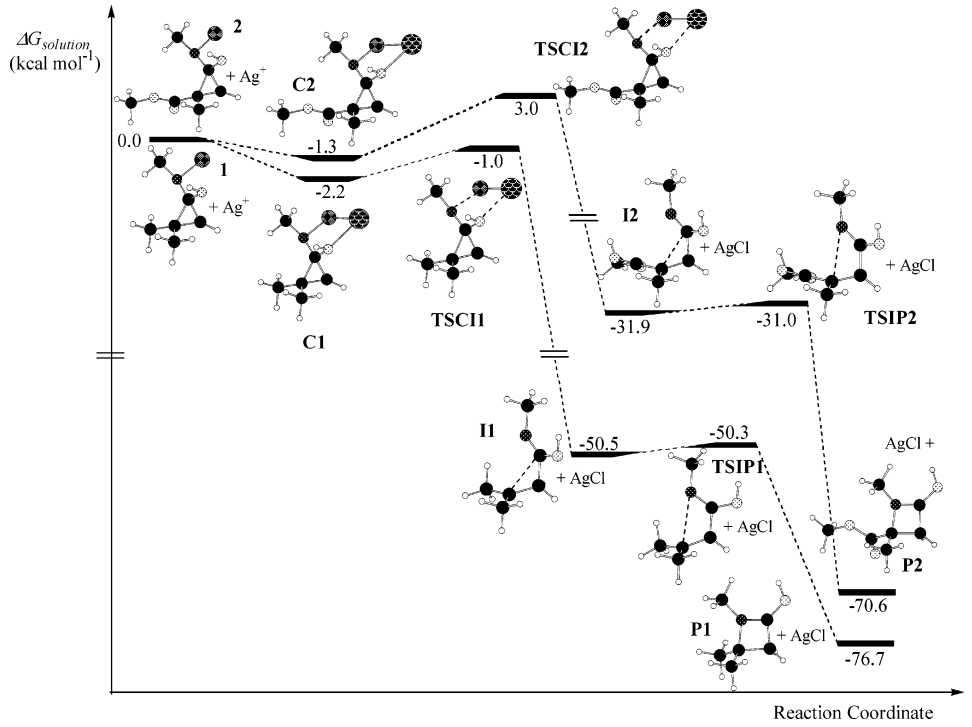

FIGURE 1. Gibbs energy profile in CH_2Cl_2 solution for the silver-assisted ring expansion of (*S*)-*N*-chloro-*N*-methyl-2,2-dimethyl-1-hydroxycyclopropylamine and (1*S*,2*S*)-*N*-chloro-*N*-methyl-1-hydroxy-2-methoxycarbonyl-2-methylcyclopropylamine.

TABLE 1. Relative B3LYP/6-31+G(d) (LANL2DZ Pseudopotential with a Set of Extra *f* Functions for Ag), Electronic Energies (Including ZPVE), Δ*G* in the Gas Phase, Δ*G* of Solvation, and Δ*G* in Solution (all in kcal mol^{-1}) of the Structures Located for the Reactions Studied in This Work (See Scheme 3)

structures	ΔE_{elec}	$\Delta G_{gas-phase}$	$\Delta G_{solvation}$	$\Delta G_{solution}$
$R^1 = R^2 = Me$				
reactants (**1** + Ag^+)	0.0	0.0	−71.5	0.0
C1	−41.6	−33.7	−40.0	−2.2
TSCI1	−40.9	−33.1	−39.4	−1.0
I1 + AgCl	−66.3	−71.5	−50.5	−50.5
TSIP1 + AgCl	−66.2	−70.7	−51.1	−50.3
P1 + AgCl	−93.0	−96.7	−51.6	−76.7
$R^1 = CO_2Me$, $R^2 = Me$				
reactants (**2** + Ag^+)	0.0	0.0	−73.5	0.0
C2	−36.8	−29.3	−45.5	−1.3
TSCI2	−34.7	−27.5	−43.0	3.0
I2 + AgCl	−50.9	−56.2	−49.2	−31.9
TSIP2 + AgCl	−50.8	−55.0	−49.5	−31.0
P2 + AgCl	−87.1	−91.4	−52.8	−70.6
$R^1 = Me$, $R^2 = CO_2Me$				
reactants (**3** + Ag^+)	0.0	0.0	−72.5	0.0
C3	−38.7	−30.8	−41.6	0.2
TSCI3	−35.5	−28.2	−39.2	5.1
I3 + AgCl	−52.1	−58.2	−50.8	−36.5
TSIP3 + AgCl	−52.0	−57.0	−51.2	−35.7
P3 + AgCl	−87.0	−91.1	−52.8	−71.4

stated we will present in the text relative Gibbs energies in solution.

Our theoretical results predict that the silver-induced ring expansion of **1** is a regioselective process, in agreement with experimental findings,[4] yielding protonated *N*-methyl-4,4-dimethyl-2-azetidinone and AgCl through a two-step mechanism.[20] First a pre-reactive complex, **C1**, between Ag^+ and **1** is formed 2.2 kcal mol^{-1} more stable than separate reactants. This complex transforms into a nitrenium ion intermediate, **I1**, 50.5 kcal mol^{-1} more

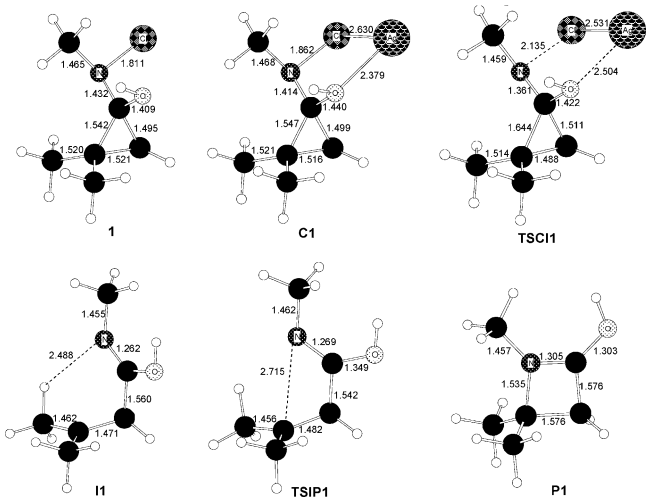

FIGURE 2. B3LYP-optimized geometries of the structures located for the formation of *N*-methyl-4,4-dimethyl-2-azetidinone.

stable than reactants through a TS **TSCI1**, 1.2 kcal mol^{-1} above the pre-reactive complex, for the extrusion of AgCl. In this nitrenium intermediate the C1−C2 bond is completely broken with no bond critical point appearing between these atoms. A bond critical point was found between the N atom and the closest hydrogen of one of the methyl substituents at C2 indicating the existence of a hydrogen bond interaction between these atoms.

A ring critical point was also located in the middle of the N−C1−C3−C2−C(methyl)−H(methyl) moiety. The

(20) We report the results obtained for the (*S*) diastereoisomer of *N*-chloro-*N*-methyl-1-hydroxy-2,2-dimethylcyclopropylamine. The process for the (*R*) diastereoisomer presents a Gibbs energy barrier for AgCl extrusion 2.4 kcal mol^{-1} larger.

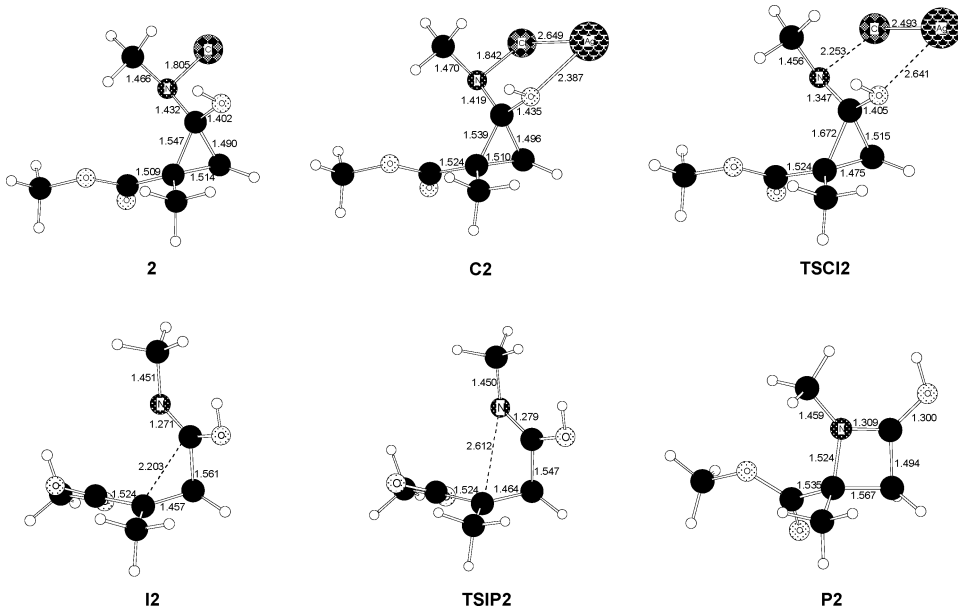

FIGURE 3. B3LYP-optimized geometries of the structures located for the formation of (*S*)-*N*-methyl-4-methoxycarbonyl-4-methyl-2-azetidinone.

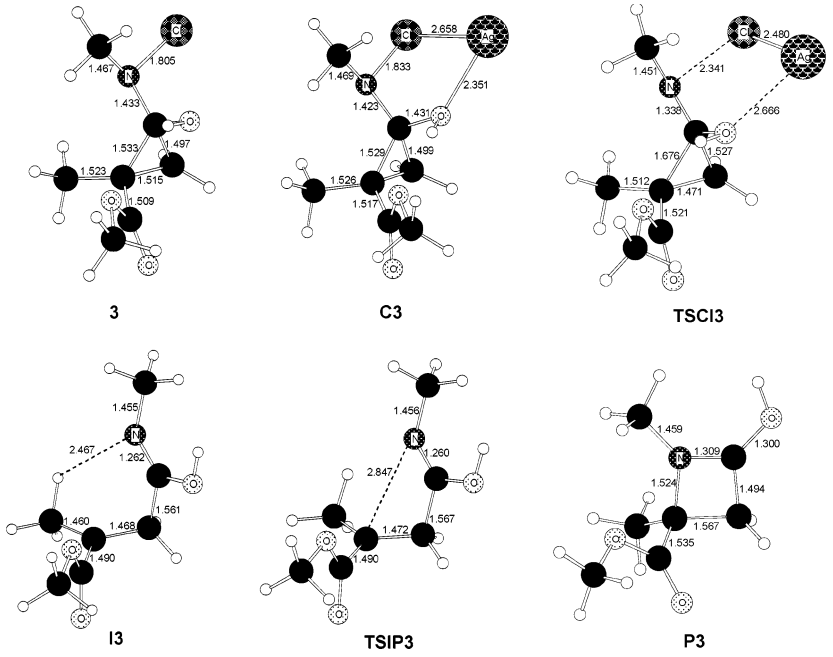

FIGURE 4. B3LYP-optimized geometries of the structures located for the formation of (*R*)-*N*-methyl-4-methoxycarbonyl-4-methyl-2-azetidinone.

nitrenium intermediate evolves into the final β-lactam through the TS **TSIP1** for rotation about the C1−C3 bond of the cyclopropyl moiety and ring closure by formation of the C4−N β-lactam bond. The N···H−C contact present in the nitrenium intermediate persists in this TS. **TSIP1** is 50.3 kcal mol^{-1} more stable than separate reactants and determines a lifetime[21] for the intermediate **I1** of 2.3×10^{-13} s. Although the magnitude of the energy barrier corresponding to the lifetime of the nitrenium intermediate (0.2 kcal mol^{-1}) is outside the accuracy range of theoretical calculations, the analysis of the topology of the PES clearly indicates the presence of such a stable structure along the electronic density rearrangement taking place after AgCl separation. The process is exothermic by 76.7 kcal mol^{-1}.

The silver-induced ring expansions of the two diastereoisomers (1*S*,2*S*)-*N*-chloro-*N*-methyl-1-hydroxy-2-methoxycarbonyl-2-methylcyclopropylamine (**2**) and (1*S*,2*R*)-*N*-chloro-*N*-methyl-1-hydroxy-2-methoxycarbonyl-2-methylcyclopropylamine (**3**) are also regioselective processes yielding the corresponding protonated *N*-methyl-4-

(21) The mean life of the nitrenium intermediates was estimated as $\tau = 1/k$, where k is the kinetic constant for its transformation into the final product. k was computed by using the conventional transition state theory $k = (k_B T/h)\ \exp(-\Delta G^{\#}/RT)$, where $\Delta G^{\#}$ is the Gibbs energy barrier.

methoxycarbonyl-4-methyl-2-azetidinones + AgCl. These reactions proceed through a two-step mechanism analogous to that for **1**. According to our calculations **2** is 0.8 kcal mol^{-1} more stable than **3**. The pre-reactive complex between Ag^+ and **2** is 1.3 kcal mol^{-1} more stable than separate reactants. The TS for AgCl extrusion, **TSCI2**, is of a later nature (AgCl more separated and C1−C2 more stretched) than **TSCI1** and is 3.0 kcal mol^{-1} less stable than reactants owing to the withdrawing character of the CO_2Me substituent. The nitrenium intermediate, **I2**, now presents a lifetime[21] of 7.3×10^{-13} s. This process is exothermic by 70.6 kcal mol^{-1}.

Although Ag^+ interacts with **3** to form a pre-reactive complex in terms of electronic energy this stable structure is not present on the Gibbs energy profile in solution (see Table 1). The TS for AgCl extrusion, **TSCI3**, has an energy barrier of 5.1 kcal mol^{-1} and evolves through a nitrenium intermediate, **I3**, about 36.5 kcal mol^{-1} more stable than separate reactants and with a lifetime[21] of 6.2×10^{-13} s with respect to its transformation into the final product **P3**. In this intermediate a N···H−C contact and a ring critical point were located analogous to those found in **I1**. The process is exothermic by 71.4 kcal mol^{-1}.

Therefore, our calculations predict that the CO_2Me substituent makes the cyclopropylamine moiety a worse donor compared to the case of two methyl substituents thus hindering the separation of AgCl. Nevertheless, the resulting rate-determining TSs are only 3.0 and 5.1 kcal mol^{-1} above the reactants rendering this mechanistic route very favorable kinetically. Thus according to our results the synthesis of 3-unsubstituted 4-methoxycarbonyl-4-methyl-2-azetidinones along this new route would be a very favorable process yielding a regio- and stereoselective product.

Conclusions

The synthesis of 3-unsubstituted 4,4-disubstituted β-lactams by silver-induced ring expansion of the corresponding 2,2-disubstituted *N*-chloro-1-hydroxycyclopropylamines is according to theoretical calculations a very efficient process yielding a regio- and stereoselective product. This process presents a two-step mechanism proceeding through a nitrenium intermediate. The rate-determining step corresponds to the extrusion of AgCl. This pathway could be an interesting new synthetic route for obtaining the useful 3-unsubstituted 4-alkoxycarbonyl-4-alkyl-2-azetidinones.

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Supporting Information Available: Absolute electronic energies, zero point vibrational energies, and Cartesian coordinates of optimized geometries of all the critical structures located along the reaction coordinate. This material is available free of charge via the Internet at http://pubs.acs.org.

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