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Theoretical Investigation on TMSOTf-Promoted Cascade Reaction of Propargyl Alcohol and Protected Tryptamine to Construct Hexahydropyrrolo-[2,3-b]Indoline

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Abstract

The first theoretical investigation on TMSOTf-promoted cascade reaction of propargyl alcohol and protected tryptamine was provided by our DFT calculation. First, propargyl alcohol is activated by TMSOTf resulting in silyl ether accompanied by release of triflic acid. Then silyl ether undergoes Meyer-Schuster re-arrangement generating allenic intermediate and HOSiMe3. Hydroxyl is transferred from the latter to ter-minal alkyne carbon along with recovered TMSOTf. Subsequently, the regioselective C-3 nucleophilic addi-tion proceeds with indole ring of tryptamine furnishing four-membered ring. Next, 5-exo-trig cyclization occurs forming fused pyrrolo[2,3-b]indoline core with simultaneous opening of four-membered ring. At last, the keto-enol tautomerization forges quaternary C-3 stereocenter through two times of proton transfer for product hexahydropyrrolo[2,3-b]indoline. Comparatively, S_N2 type 5-exo-trig cyclization forming five-membered ring is determined to be rate-limiting.

Keywords: TMSOTf; Meyer-Schuster Rearrangement; C-3 Nucleophilic Addition; 5-Exo-Trig Cyclization; Indole

Introduction

As privileged central entities, indole-based heterocycles and derivatives are frequently encountered in drug discovery and natural product synthesis due to their broad spectrum of biological activity [1-3]. These structural motifs are crucial in multiple scientific domains especially pyrrolo[2,3-b]indoline core, which bears qua-ternary carbon center at C-3a position and constitutes wide-ranging complex alkaloid frameworks [4, 5]. Thus, the generation of pyrrolo[2,3-b]indoline has received considerable attention such as reconstruction of pyr-rolo[2,3-b]indoles carrying an α-configured reverse C3-dimethylallyl moiety by using recombinant enzymes [6]. In past few decades, many progresses have been achieved highlighting diverse reactivity of indole system. Kale reported Ca(II)-catalyzed cascade reaction of tryptamines with propargylic alcohols by tempera-ture-driven ring opening and closing *via* the allene migration pathway [7]. Then they gave Calci-um(II)-catalyzed [2+3] annulation of enynones *via* sustainable approach to 9H-pyrrolo[1,2-a] indole frame-works [8]. Chen discovered 3a-benzoylmethyl pyrrolidino[2,3-b]indolines *via* CuII-catalyzed radical annulation/C3-functionalization sequence [9]. Corrieri researched practical and sustainable preparation of pyrrolo [2,3-b]indoles by Cu/Fe catalyzed intramolecular C(Sp2)–H amination [10].

Chen summarized rearrangement reactions as powerful tools for functional group interconversion [11]. Wu researched radical-mediated rearrangements to reorganize molecular connectivity under mild conditions in natural product synthesis [12]. Engel exploited site-selective new carbon heteroatom bond formation for the synthesis of a,b-unsaturated carbonyl compounds [13]. Recently, Vidari and Zheng explored mild, selective boronic acid catalyzed 1,3-transposition of allylic alcohols and Meyer-Schuster Rearrangement of Pro-pargylic Alcohols [14, 15]. In addition, Bandini found catalytic functionalization of indoles in a new dimension together with Zhou's asymmetric synthesis of oxindoles bearing a tetrasubstituted stereocenter at the C-3 position [16, 17]. Breneman obtained charge, energy redistribution in sulfonamides undergoing conformational changes and hybridization as controlling influence over conformer stability [18, 19]. On the other, "am-ide resonance" correlates with a breadth of C–N rotation barriers, which may cause more planarity at nitrogen in strong donation thereby destabilize key intermediates [20].

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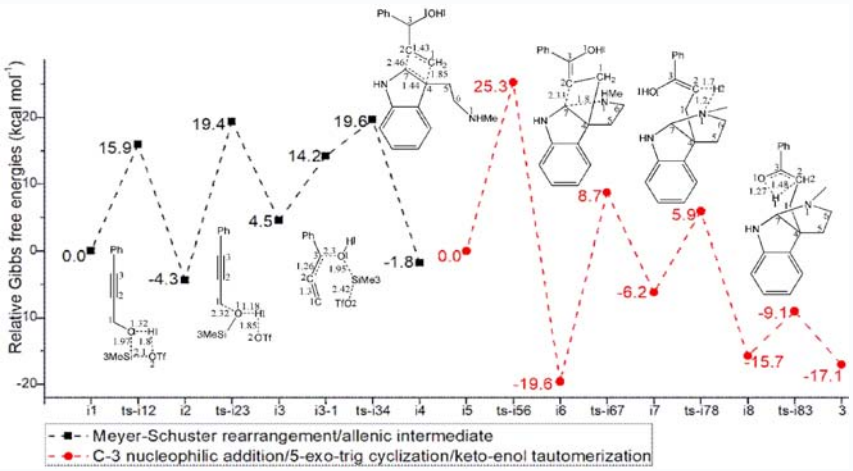


Figure 1: Relative Gibbs free energy profile in solvent phase starting from complex i1, i5 (Bond lengths of optimized TSs in Å).

Based on previous investigations such as TMSOTf-promoted cyclization of in-dole-2-methyl-A-aminoketones to access 4-aryl-substituted b-carbolines of Yang [21], another breakthrough was TMSOTf-promoted cascade reaction of propargyl alcohol and protected tryptamine of Rivonker [22]. This approach was approved with good functional group tolerance and efficient leading to desired product. Although hexahydropyrrolo-[2,3-b]indoline was constructed *via* Lewis-acid-driven annulation strategy, how propargyl alcohol was activated by TMSOTf resulting in formation of silyl ether accompanied by release of triflic acid [23]? Furthermore, how Meyer-Schuster-type rearrangement was catalyzed by TfOH generating reactive allenic intermediate [24]? What's the concrete process including regioselective C-3 nucleophilic addition of the indole ring from tryptamine, subsequent 5-exo-trig cyclization [25] eventually forging fused pyr-rolo[2,3-b]indoline core with a quaternary C-3 stereocenter? How nitrogen-containing molecule was acquired through final keto-enol tautomerization favored thermodynamically?

Computational Details

Structures were optimized at M06-2X/6-31G(d) level with GAUSSIAN09 [26]. Among various DFT methods [27], M06-2X functional has smaller deviation between experimental and calculated value than B3LYP hybrid functional [28, 29]. With 6-31G(d) basis set, it can provide best compromise between time consumption and energy accuracy. It was also found to give accurate results for stepwise (2+2) cycloaddition, enantioselective (4+3) and Diels-Alder reaction [30, 31]. Together with good performance on noncovalent interaction, it is suitable for this system [32-34]. To obtain Zero-Point Vibrational Energy (ZPVE), harmonic frequency calculations were carried out at M06-2X/6-31G(d) level gaining thermodynamic corrections at 333 K and 1 atm in 1,2-dichloroethane (DCE). At M06-2X/6-311++G(d,p) level, the solvation-corrected free energies were obtained using Integral Equation Formalism Polarizable Continuum Model (IEFPCM) [35-39] on M06-2X/6-31G(d)-optimized geometries. NBO procedure was performed with Natural bond orbital (NBO3.1) obtaining lone pair and bond to characterize bonding orbital interaction and electronic properties [40-42]. Using Multiwfn_3.7_dev package [43].

Results and Discussion

The mechanism was explored for TMSOTf-promoted cascade reaction of propargyl alcohol 1 and protect-ed tryptamine 2 leading to hexahydropyrrolo-[2,3-b]indoline 3 (Scheme 1). As illustrated by Scheme 2, initially, the propargyl alcohol 1 is activated by TMSOTf resulting in silyl ether accompanied by release of triflic acid TfOH. Then silyl ether undergoes Meyer-Schuster rearrangement catalyzed by TfOH generating reactive allenic intermediate and $HOSiMe_3$. The latter could transfer hydroxyl to terminal alkyne carbon along with re-covered TMSOTf. Subsequently, the regioselective C-3 nucleophilic addition proceeds with indole ring of tryptamine 2 furnishing four-membered ring. Next, 5-exo-trig cyclization occurs forming fused pyr-rolo[2,3-b]indoline core involving sulfonamide nitrogen concurrently with opening of four-membered ring. Finally, the keto-enol tautomerization forges quaternary C-3 stereocenter of hexahydropyrrolo[2,3-b]indoline 3 through two proton transfer. Figure 1 listed schematic structures of optimized TSs in Scheme 2. Table 1 gave activation energy for all steps.

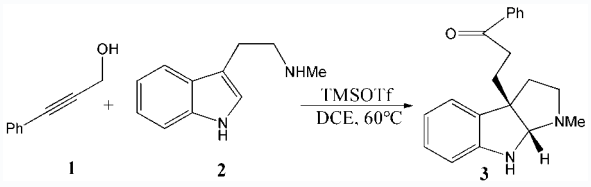
TS is Named According to the Two Intermediates it Connects

Meyer-Schuster rearrangement/allenic intermediate

Initially, the first complex i1 is formed binding TMSOTf and propargyl alcohol 1 as starting point of step 1 (black dash line of Figure 1). 1 was activated through deprotonation of TMSOTf *via* ts-i12 with the activation energy of 15.9 kcal mol^{-1} exothermic by -4.3 kcal mol^{-1} resulting in i2. The transition vector corresponds to cleavage of hydroxyl group O1···H1 and Si···O2 single bond as well as bonding of Si···O1, H1···O2 (1.32, 2.1, 1.97, 1.8 Å). Once proton H1 is captured by DMSOTf, triflic acid TfOH is produced as catalyst of next step, the release of which is accompanied by formation of silyl ether.

Then assisted by TfOH, silyl ether undergoes Meyer-Schuster rearrangement *via* ts-i23 with increased activation energy of 23.7 kcal mol^{-1} in step 2 endothermic slightly by 4.5 kcal mol^{-1} leading to i3. The transition vector is complicated involving breaking of C1···O1, H1···O2 and reconnection of O1···H1 as hydroxyl group for new $HOSiMe_3$ (2.32, 1.85, 1.18 Å) (Figure S1a). Concurrently, the reactive allenic intermediate is generated without $HOSiMe_3$ when single C1-C2, triple C2-C3 bond both turns to be double one.

The intermediate i3 could present another binding form as i3-1, which is more reactive with increased relative energy of 9.7 kcal mol^{-1}.



Scheme 1: TMSOTf-promoted cascade reaction of propargyl alcohol 1 and protected tryptamine 2 leading to hexahy-dropyrrolo-[2,3-b]indoline 3.

Subsequently from i3-1, hydroxyl O1H1 was donated by $HOSiMe_3$ to terminal alkyne carbon C3 *via* ts-i34 in step 3 with small activation energy of 5.4 kcal mol^{-1} exothermic by -1.8 kcal mol^{-1} giving i4. The transition vector of TfO2···Si···O1···C3 not only denotes hydroxyl group was leaving Si, approaching C3 but recovery of TMSOTf (2.42, 1.95, 2.3 Å) (Figure S1b). The C3-O1 is available in i4 as enhanced single bond together with typical C1=C2 double one.

C-3 nucleophilic addition/5-exo-trig cyclization/keto-enol tautomerization

After removal of TMSOTf and addition of tryptamine 2, the complex i5 is formed as starting point of step 4 (red dash line of Figure 1). The regioselective C-3 nucleophilic addition proceeds *via* ts-i56 with activation energy of 25.3 kcal mol^{-1} exothermic by -19.6 kcal mol^{-1} affording stable i6. The transition vector corresponds to linkage of two directions that is C1···C4, C2···C7 as well as stretching of C1=C2 double in allenic intermediate and C4=C7 in indole ring of tryptamine 2 as single one (1.85, 2.46, 1.43, 1.44 Å) (Figure S1c). The formation of C1-C4, C2-C7 furnish four-membered ring and resultant C2=C3 of i6.

Next, the 5-exo-trig cyclization occurs *via* ts-i67 with increased activation energy of 28.3 kcal mol^{-1} in step 5 exothermic by -6.2 kcal mol^{-1} leading to i7. The transition vector is complicated involving S_N2 type linkage and breaking as N1···C7···C2 (1.8, 2.33 Å) (Figure S1d). *Via* this atmoic motion, the five-membered ring forms for fused pyrrolo[2,3-b]indoline core involving sulfonamide nitrogen

Table 1: The activation energy (in kcal mol^{-1}) of all reactions in gas and solvent.

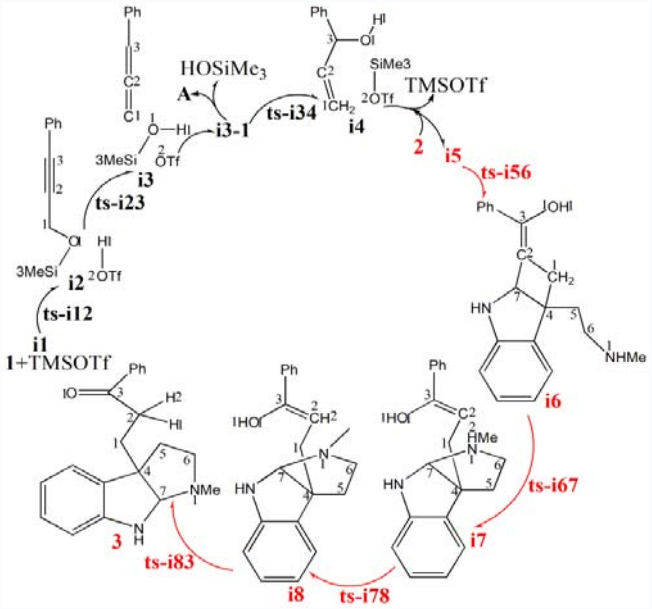
TS	$\Delta G^{\neq}_{gas}$	$\Delta G^{\neq}_{sol}$
ts-i12	22.67	15.90
ts-i23	31.79	23.72
ts-i34	7.88	5.44
ts-i56	30.11	25.25
ts-i67	32.86	28.36
ts-i78	18.06	12.14
ts-i83	9.52	6.68

with simultaneous opening of four-membered ring. It is noted that in stable i7, mediate C2 is still sp2 hybrid with no hydrogen on it.

At last, the keto-enol tautomerization takes place through two times of proton transfer. *Via* ts-i78 in step 6, the proton H2 transfer from N1 to C2 as N1···H2···C2 (1.2, 1.7 Å) with activation energy of 12.1 kcal mol^{-1} exothermic by -15.7 kcal mol^{-1}. Then another proton H1 transfer from O1 to C2 as O1···H1···C2 (1.27, 1.48 Å) *via* ts-i83 with decreased activation energy of 6.6 kcal mol^{-1} exothermic continuously by -17.1 kcal mol^{-1} in final step 7. Two protons bonded on C2 makes it turn to be sp3 hybrid, which forges quaternary C-3 stereocenter of product hexahydropyrrolo[2,3-b]indoline 3. Comparatively, the S_N2 type 5-exo-trig cyclization together with four-membered ring opening in step 5 is determined to be rate-limiting for DMSOTf-promoted cascade reaction of propargyl alcohol and protected tryptamine to hexahydropyrrolo-[2,3-b]indoline.

Conclusions

In summary, the first theoretical investigation was provided by our DFT calculation on TMSOTf-promoted cascade reaction of propargyl alcohol and protected tryptamine. First, propargyl alcohol is activated by TMSOTf resulting in silyl ether accompanied by release of triflic acid TfOH. Then silyl ether undergoes Meyer-Schuster rearrangement catalyzed by TfOH generating reactive allenic intermediate and $HOSiMe_3$. Hydroxyl is transferred from



Scheme 2: Proposed reaction mechanism of TMSOTf-promoted cascade reaction of 1 and 2 leading to 3. TS is named according to the two intermediates it connects.

the latter to terminal alkyne carbon along with recovered TMSOTf. Subsequently, the regioselective C-3 nucleophilic addition proceeds with indole ring of tryptamine furnishing four-membered ring. Next, 5-exo-trig cyclization occurs forming fused pyrrolo[2,3-b]indoline core involving sulfonamide nitrogen with simultaneous opening of four-membered ring. At last, the keto-enol tautomerization forges quaternary C-3 stereocenter through final two times of proton transfer for product hexahydropyrrolo[2,3-b]indoline. Comparatively, S_N2 type 5-exo-trig cyclization forming five-membered ring in step 5 is determined to be rate-limiting.

Electronic Supplementary Material

Supplementary data available: [Computation information and cartesian coordinates of stationary points; Calculated relative energies for the ZPE-corrected Gibbs free energies (ΔG_{gas}), and Gibbs free energies (ΔG_{sol}) for all species in solution phase at 333 K.]

Author Contributions

Conceptualization, Nan Lu; Methodology, Nan Lu; Software, Nan Lu; Validation, Nan Lu; Formal Analysis, Nan Lu; Investigation, Nan Lu; Resources, Nan Lu; Data Curation, Nan Lu; Writing-Original Draft Preparation, Nan Lu; Writing-Review & Editing, Nan Lu; Visualization, Nan Lu; Supervision, Nan Lu; Project Administration, Nan Lu. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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