Theoretical investigation on synthesis of fused [1,2,3]-triazoloheteroarene via DBU-catalyzed intramolecular azo annulation and 3,4,5-trisubstituted [1,2,4]-triazole via I₂-catalyzed cycloaddition

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Abstract: The mechanism is investigated for DBU-catalyzed intramolecular azo annulation of N-tosylhydrazone and I₂-catalyzed cycloaddition of phenyl tosyl hydrazone with N-phenylbenzamidine. The former contains rate-limiting α-elimination of tosylate facilitated by DBU affording amphiphilic nitrene and intramolecular, 5-endo-trig cyclization forming [1,2,3]-triazoloheteroarene. This method is also applicable for other nonpyridine heteroarene based on enhanced activity of DBU. The latter is composed of eight steps including activation of hydrazone mediated by I₂, nucleophilic addition of amide, intramolecular electron transfer via two times of proton transfer, intramolecular nucleophilic attack followed by third proton transfer achieving ring closure and final reductive elimination of HI, TsNH₂ yielding 3,4,5-trisubstituted [1,2,4]-triazole. The rate-limiting step is intramolecular electron transfer under I₂ catalysis. The positive solvation effect is suggested by decreased absolute and activation energies in solution compared with in gas. These results are supported by Multiwfn analysis on FMO composition of specific TSs, and MBO value of vital bonding, breaking.

Keywords: triazole; azo annulation; N-tosylhydrazone; amidine; 5-endo-trig

1. Introduction

As building blocks of essential amino acids, nitrogen-containing five-membered heterocycles are indispensable to life’s sustenance. Triazolopyridines [1], characterized by triazole connecting with pyridine ring are crucial in numerous fields including molecular recognition, medicine, and biology [2]. The structures of 1,2,3-triazole and 1,2,4-triazole can be differentiated based on the arrangement of nitrogen and type of ring fusion. The general utility of [1,2,3]-triazolopyridine was attractive in improving metal-ligand selectivity and structure-activity relationship [3]. Gevorgyan used Rh-catalyzed insertion/denitrogenation in construction of [1,2,3]-triazolo synths and Cu-catalyzed transannulation in synthesis of indolizines [4,5]. Driver described Ni-catalyzed alkenylation of triazolopyridines leading to 2,6-disubstituted pyridines [6]. Nagasawa reported Cu(II)-catalyzed oxidative N–N bond formation between pyridyl N and adjacent hydrazone [7]. Zhu achieved metal- and azide-free oxidative coupling to construct C–C and C–P bonds [8]. Tedder reported three-step protocol in preparation of [1,2,3]-triazolo quinolines by invoking Kornblum oxidation [9].

On the other hand, 3,4,5-trisubstituted 1,2,4-triazoles are vital structural and functional motifs as pharmaceutical compounds [10,11]. They are also useful in preparation of many drug molecules with broad biological activity [12,13]. Many
efforts were devoted to 3,4,5-trisubstituted 1,2,4-triazoles in past few decades. The direct C–H arylation of 1,2,4-triazoles and 1,3,4-oxadiazoles with aryl iodides was mediated by ligand-free Cu(0) [14]. The construction of its derivatives was also reported via cyclocondensation of alkylidene dihydropyridine and aryl diazonium [15]. The reaction of isothiocyanates with various hydrazine reagents was demonstrated to form this structural scaffold through multistep [16]. Recently, the synthesis of symmetrical and unsymmetrical 3,4,5-triaryl-1,2,3-triazoles was disclosed by B(C₆F₅)₃-catalyzed dehydrogenative cyclization of N-tosylhyrazones and anilines via combined experimental and computational investigation [17]. A three-component ugi-type reaction of N-carbamoyl imines N-isocyaniminotriphenylphosphorane (NIITP) and carbonyl compounds could enable a broad scope primary α-amino 1,3,4-oxadiazole synthesis [18]. However, the limits in either starting materials, multisteps or complicated catalysts restrict the scope and application of these methods. To develop approaches utilizing simple and cheap starting materials, amidines are highly desired in the synthesis of various 1H-1,2,4-triazoles, 3,5-disubstituted, 1,3-disubstituted and 1,3,5-trisubstituted 1,2,4-triazoles [19].

The intermolecular [3 + 2] dipolar cycloaddition was reported by Carrick group affording 1,2-pyrazole in modest regioselectivity incorporating monosubstituted 1,2,4-triazinyl-pyridine with N-tosylhydrazone [20]. Then a Kornblum-type reaction was completed leading to heteroaryl-1,3,4-oxadiazole [21]. On the basis of this, a serendipitous breakthrough of them was [1,2,3]-triazolo-heteroarene from N-tosylhydrazone with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as potential initiator [22]. Compared with this was synthesis of 1,2,4-triazolo[4,3-a]pyridine via oxidative coupling of 2-aminopyridine with N-tosylhydrazone and electrochemical cyclization to access trisubstituted 1,2,4-triazole of Li group [23,24] especially their I₂-catalyzed construction of 3,4,5-trisubstituted 1,2,4-triazole under air atmosphere [25]. Although 1,2,3-pyridyltriazole and 3,4,5-trisubstituted 1,2,4-triazole were obtained, there is no report about detailed mechanistic study explaining 5-endo-trig cyclization. How the activity of DBU was enhanced compared with morpholine or metal-mediated strategies in azo annulation? What is the real catalytic cycle of I₂ in cycloaddition of N-functionalized amidine with hydrazone? To solve these puzzled problems in experiment, an in-depth theoretical study was necessary for these methods leading to various functionalized triazole.

2. Computational details

The geometry optimizations were performed at the B3LYP/BSI level with the Gaussian 09 package [26,27]. The mixed basis set of LanL2DZ for I and 6-31G(d) for other non-metal atoms [28–32] was denoted as BSI. Different singlet and multiplet states were clarified with B3LYP and ROB3LYP approaches including Becke’s three-parameter hybrid functional combined with Lee-Yang-Parr correction for correlation [33,34]. The nature of each structure was verified by performing harmonic vibrational frequency calculations. Intrinsic reaction coordinate (IRC) calculations were examined to confirm the right connections among key transition-states and corresponding reactants and products. Harmonic frequency
calculations were carried out at the B3LYP/BSI level to gain zero-point vibrational energy (ZPVE) and thermodynamic corrections at 353 K, 363 K and 1 atm for each structure in toluene and chlorobenzene. The solvation-corrected free energies were obtained at the B3LYP/6-311++G(d,p) (LanL2DZ for I) level by using integral equation formalism polarizable continuum model (IEFPCM) in Truhlar’s “density” solvation model [35–37] on the B3LYP/BSI-optimized geometries.

As an efficient method of obtaining bond and lone pair of a molecule from modern ab initio wave functions, NBO procedure was performed with Natural bond orbital (NBO3.1) to characterize electronic properties and bonding orbital interactions [38,39]. The wave function analysis was provided using Multiwfn_3.7_dev package [40] including research on frontier molecular orbital (FMO) and Mayer bond order (MBO).

3. Results and discussion

The mechanism was explored for (a) DBU-catalyzed intramolecular azo annihilation of N-tosylhydrazone 1, 3 leading to [1,2,3]-triazoloheteroarene 2, 4 (b) I2-catalyzed cycloaddition of phenyl tosyl hydrazone 5 with N-phenylbenzamidine 6 producing 3,4,5-trisubstituted [1,2,4]-triazole 7 (Scheme 1). Illustrated by black arrow of Scheme 2a, facilitated by DBU, α-elimination of tosylate TsH as leaving group from 1 affords an amphiphilic nitrene. Then product 2 is formed via intramolecular, disfavored, 5-endo-trig cyclization.

![Scheme 1](image)

Scheme 1. (a) DBU-catalyzed intramolecular azo annihilation of N-tosylhydrazone 1, 3 leading to [1,2,3]-triazoloheteroarene 2, 4; (b) I2-catalyzed cycloaddition of hydrazone 5 with N-functionalized amidine 6 producing 3,4,5-trisubstituted [1,2,4]-triazole 7.

Shown by black arrow of Scheme 2b, the activation of 5 mediated by I2 gives HI and zwitterion species, of which the nucleophilic addition of 6 generates another coupled zwitterionic pair B1. Then, B1 is transformed to species C via two times of complex proton transfer to complete intramolecular electron transfer. Subsequently, after a third simple proton transfer from species C, ring closure undergoes via intramolecular nucleophilic attack affording species D2, from which the reductive elimination of HI and TsNH2 elimination yields final product 7. The oxidization of HI to I2 by air was not considered here.

The schematic structures of optimized TSs in Scheme 2 are listed in Figure 1. The activation energy was shown in Table 1 for all steps. Supplementary Table S15, Table S16 provided the relative energies of all stationary points. According to
experiment, the Gibbs free energies in toluene and chlorobenzene solution phase are discussed here.

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

<table>
<thead>
<tr>
<th>TS</th>
<th>$\Delta G^*$$_{\text{gas}}$</th>
<th>$\Delta G^*$$_{\text{sol}}$</th>
</tr>
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<tbody>
<tr>
<td>ts-i12</td>
<td>2.71</td>
<td>1.97</td>
</tr>
<tr>
<td>ts-i23</td>
<td>18.39</td>
<td>20.32</td>
</tr>
<tr>
<td>ts-ia2</td>
<td>15.89</td>
<td>16.88</td>
</tr>
<tr>
<td>ts-i45</td>
<td>3.60</td>
<td>3.70</td>
</tr>
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<td>ts-i56</td>
<td>21.37</td>
<td>21.72</td>
</tr>
<tr>
<td>ts-ib4</td>
<td>19.53</td>
<td>20.84</td>
</tr>
<tr>
<td>ts-in12</td>
<td>6.72</td>
<td>10.65</td>
</tr>
<tr>
<td>ts-in3B</td>
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<td>16.67</td>
</tr>
<tr>
<td>ts-B12</td>
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<td>22.85</td>
</tr>
<tr>
<td>ts-B2C</td>
<td>14.87</td>
<td>20.09</td>
</tr>
<tr>
<td>ts-CD1</td>
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<td>17.61</td>
</tr>
<tr>
<td>ts-D12</td>
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<tr>
<td>ts-Din4</td>
<td>13.26</td>
<td>12.76</td>
</tr>
<tr>
<td>ts-Ein5</td>
<td>46.60</td>
<td>37.80</td>
</tr>
</tbody>
</table>

**Scheme 2.** Proposed reaction mechanism of (a) DBU-catalyzed intramolecular azo annihilation of 1 leading to 2; (b) I$_2$-catalyzed cycloaddition of 5 with 6 producing 7. TS is named according to the two intermediates it connects.
Figure 1. Relative Gibbs free energy profile in solvent phase starting from complex (a) i1, ia, i4, ib; (b) in1, in3, E (Bond lengths of optimized TSs in Å).
3.1. TsH α-elimination/intramolecular 5-endo-trig cyclization and substrate scope

The treatment of 1 with DBU forms initial complex i1, which is taken the starting point of tosylate TsH α-elimination involving two steps. The first proton capture proceeds via ts-i12 as step 1 with the activation energy of 2.0 kcal mol⁻¹ relative to the i1 (black dash line of Figure 1a). The transition vector corresponds to proton H1 transfer from N1 to N4 (1.12, 1.24 Å) (Figure S1a). Clearly this step is fairly easy facilitated by DBU, which is protonated in resultant i2 exothermic by −6.4 kcal mol⁻¹. Then DBU hands over proton to O1 of Ts making the molecule TsH as leaving group. The fracture of Ts takes place ahead of this slightly in a concert process via ts-i23 in step 2 with activation energy of 20.3 kcal mol⁻¹ leading to stable intermediate i3 continuously exothermic by −5.0 kcal mol⁻¹. The transition vector is complex including corresponding to the breaking of N1···S bond, the shortening of N1-N2 from double to third and delayed H1 transfer from N4 to O1 (2.16, 1.19, 1.04, 1.7 Å) (Figure S1b).

Without DBU and TsH, the amphiphilic nitrene ia is located as new starting point of step 3 via ts-ia2 with activation energy of 16.9 kcal mol⁻¹ and heat release of −9.7 kcal mol⁻¹ to complete intramolecular 5-endo-trig cyclization furnishing five-membered ring of final 1,2,3-pyridyltriazole 2. The transition vector contains remarkable N1-N3 bonding, cooperative C1-C2 contraction, C2-N2 and N1-N2 elongation (2.04, 1.43, 1.33, 1.17 Å) (Figure S1c). From kinetics, the leaving of Ts in step 2 is determined to be rate-limiting still under the promotion of DBU. This outcome coincides with experiment postulating DBU concentration to be rate determining.

To highlight the idea of feasibility for changes in electron density and not molecular orbital interactions are responsible of the reactivity of organic molecules, quantum chemical tool Multiwfn was applied to analyze of electron density such as molecular orbital interactions are responsible of the reactivity of organic molecules, determining.

Thus N1 and N2 turns to be positive and negative charged in in2, from which the loss of H1 and adding of 6 gives in3 as new starting point of next step.

From in3, the nucleophilic addition of 6 undergoes via ts-in3B with activation energy of 7.7 kcal mol⁻¹.
energy of 16.7 kcal mol\(^{-1}\) exothermic by \(-3.6\) kcal mol\(^{-1}\) generating another coupled zwitterionic pair B1 in step 2. With lone pair on N4 and positively charged C5, this step is readily accessible. The transition vector also indicates simple approaching of N4 to C5 (1.65 Å). The remaining I1 bonding to N1 shifts to from I1-H2⋯N4 H bond exerting more effective stabilizing effect for B1.

3.3. Intramolecular electron transfer and nucleophilic attack

The next intramolecular electron transfer required two times of complex proton transfer. The first one N6⋯H3⋯N2 is accompanied by cyclization from N6 to N1 forming five-membered ring in step 3 (1.58, 1.14, 1.33 Å) via ts-B12 with the activation energy of 22.9 kcal mol\(^{-1}\) leading to B2 exothermic by \(-15.2\) kcal mol\(^{-1}\) favorable thermodynamically. This detailed motion can be demonstrated by the transition vector of ts-B12. Then, B2 is transformed to species C via ts-B2C in step 4 with a barrier of 20.1 kcal mol\(^{-1}\) exothermic by \(-4.6\) kcal mol\(^{-1}\). The transition vector is composed of N1⋯N6 cleavage causing ring opening and laggering proton H2 transfer from N4 to N6 (1.72, 1.44, 1.16 Å). I1 is still bonded to H2. The consequence is actually proton on N4 transfer to N2 making it carrying more electrons ready for subsequent nucleophilic attack.

Before intramolecular nucleophilic attack, a third proton transfer happens via ts-CD1 with the activation energy of 17.6 kcal mol\(^{-1}\) relative to C forming stable D1 exothermic by \(-22.6\) kcal mol\(^{-1}\) in step 5. According to the transition vector (Figure S1e), this process is simple about proton H3 returning from N2 to N6 increasing the nucleophilic ability of N2, which therefore initiated the real nucleophilic attack of N2 to C3 via ts-D12 with the activation energy of 15.6 kcal mol\(^{-1}\) forming D2 exothermic by \(-17.9\) kcal mol\(^{-1}\) in step 6. A new five-membered ring is formed via N2-C3 linking as precursor of [1,2,4]-triazole. Although multisteps are demanded, barriers of them are all mediate especially with continuous heat release favorable from thermodynamics.

3.4. Reductive elimination of HI and TsNH\(_2\) elimination

The reductive elimination of HI proceeds via ts-Din4 from D2 with the activation energy of 12.8 kcal mol\(^{-1}\) enormously exothermic by \(-42.3\) kcal mol\(^{-1}\) in step 7 forming in4 rather stable. The transition vector denotes proton H4 on C5 transferring to I1 and concert breaking of N1-I1 bond (1.21, 1.98, 2.36 Å) producing HI leaving group. Once HI is left, the double bond shifts from N1-N2 to C5-N1 in species E as the last starting point of step 8. Via ts-Ein5, the elimination of TsNH\(_2\) is achieved with a barrier of 37.8 kcal mol\(^{-1}\) exothermic by \(-21.2\) kcal mol\(^{-1}\) liberating in5 through concerted cleavage of N2⋯S, C3⋯N6, and N6-S linkage (2.32, 1.61, 1.92 Å) according to the transition vector (Figure S1f). The final product 3,4,5-trisubstituted [1,2,4]-triazole 7 is obtained with the departure of TsNH\(_2\) and N2-C3 bond shortening from single to double. Without promotion of I\(_2\) catalyst, the barrier of last step is elevated normally.

Considering I\(_2\) catalysis, the intramolecular electron transfer is determined to be rate-limiting. Although barriers of step 2, step 3 and step 8 are somewhat high yet all capable to overcome under the experimental temperature of 90 °C. Especially,
facilitated by chlorobenzene solution, the positive solvation effect significantly reduced activation energies compared with in gas phase. The above analysis was also verified by MBO results and atomic orbital contribution to HOMO of typical TSs (Table S17, Figure S2).

4. Conclusions

Our DFT calculations provide the first theoretical investigation on DBU-catalyzed intramolecular azo annulation of N-tosylhydrazone. Facilitated by DBU, the tosylate α-elimination affords an amphiphilic nitrene via two steps with the second to be rate-limiting. The [1,2,3]-triazoloheteroarene is formed via intramolecular, 5-endo-trig cyclization. The analysis of substrate scope approves the applicability of this method for other nonpyridine heteroarene based on enhanced activity of DBU.

For I₂-catalyzed cycloaddition of phenyl tosyl hydrazone with N-phenylbenzamidine, the activation of hydrazone mediated by I₂ gives HI and zwitterion species. The nucleophilic addition of amidine generates coupled zwitterionic pair, which completes intramolecular electron transfer via two times of proton transfer. After a third proton transfer, ring closure undergoes via intramolecular nucleophilic attack. The reductive elimination of HI and TsNH₂ elimination yields final 3,4,5-trisubstituted [1,2,4]-triazole. The rate-limiting step is intramolecular electron transfer under I₂ catalysis.

The positive solvation effect is suggested by decreased absolute and activation energies in toluene and chlorobenzene solution compared with in gas especially the latter. These results are supported by Multiwfn analysis on FMO composition of specific TSs, and MBO value of vital bonding, breaking.

Supplementary materials: 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 353 K, 363 K].

Author contributions: Conceptualization, NL; methodology, NL; software, NL; validation, NL; formal analysis, NL; investigation, NL; resources, NL; data curation, NL; writing—original draft preparation, NL; writing—review and editing, NL; visualization, NL; supervision, CM; project administration, CM; funding acquisition, CM. 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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