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Theoretical Investigation on TfOH Catalyzed Cascade Cyclization Reaction with Conjugated 1,5-Enyneto Construct Benzo[b]-Fluorenone and Benzo[de]Anthracen-7-One

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Abstract

Our DFT calculation provided the first theoretical investigation on TfOH-mediated cascade cyclization from ethyl (E)-2-(2,3-diphenyl-1H-inden-1-ylidene)acetate. The triple bond was activated via protonation forming carbocation intermediate followed by rate-limiting 6-endo-dig cyclization resulting in six-membered ring. The naphthalene ester was generated via aromatization and concomitant recover of TfOH. The ester group is activated under acidic condition, from which two paths are competitive not only from similar barriers but relative energy of counterparts. One is intramolecular acylation from the first aromatic ring followed by dealcoholation producing major benzofluorenone product. The alternative from counterpart is via retro-Friedel–Crafts C–C cleavage and subsequent intramolecular acylation by a third aryl ring furnishing another benzo[de]anthracen-7-one product.

Keywords: Benzofluorenone; Cascade Cyclization; 1,5-Enyne; 6-Endo-Dig; Intramolecular Acylation

Introduction

As promising motifs in organic synthesis, enyne moieties can undergo cyclization to form polycyclic skeleton through acid-facilitated selective π activation. For instance, Aguilar researched 1,3-Dien-5-Ynes as versatile building blocks for carbo- and heterocycles [1]. Pradhan explored intermolecular allene–alkyne coupling [2]. Trost reported transition metal-catalyzed couplings of alkynes to 1,3-enynes [3]. Goel discovered a rapid access to fused polycyclic products via acid-triggered cascade cyclization of enynes [4]. In addition, fluorinated fluorenone was obtained from 1,6-Enynes mediated by Cu(0)/selectfluor system involving C-C single bond cleavage [5]. The fulvenes were synthesized from C1–C5 cycloaromatization in triplet state antiaromaticity relief and self-terminating photorelease of formaldehyde [6]. There is also Brønsted/Lewis Acid-promoted site-selective intramolecular cycloisomerizations of aryl-fused 1,6-diyn-3-ones [7]. In this field, 6-endo-dig cyclizations of 1,5-enyne was used to assemble complex carbocyclic and aromatic scaffolds [8,9]. By protonation, this method proceeds through π activation of alkyne leading to carbocation and regioselective ring [10].

Major achievements are Alabugin's synthesis of Bu3SnH-functionalized indenes via chemoselective radical-mediated transformation of 1,5-enyne [11, 12] and equivalent alkenes in radical cascades to overcome stereoelectronic restriction on ring expansion for preparation of expanded polyaromatics [13]. Recently, Liu reported Au(I)-catalyzed 6-endo-dig cyclization of aromatic 1,5-enynes Leading to 2-(Naphthalen-2-Yl)Anilines [14]. Although many advances have been achieved to explore 1,5-enyne moieties, efficient approach is still desirable to uncover TfOH-mediated cascade reaction of conjugated 1,5-enyne to deliver benzo[b]fluorenone scaffold. In this context, Benzo-[b]fluorenone and its viable derivatives represent core structure of natural bioactive products such as organic light-emitting diodes, materials science, and semiconductors [15-17]. Considering the significance of benzo[b]fluorenone motif, Kishore *group* developed access to benzo[a]fluorenes, benzo[b]fluorenes, and indenes triggered by simple Lewis acid [18]. Goel discovered two-step to fused-/spiro-polycyclic frameworks via double Heck cascade [19]. Akbar demonstrated iodine-mediated synthesis of benzo[a]fluorenone from yne-enone [20].

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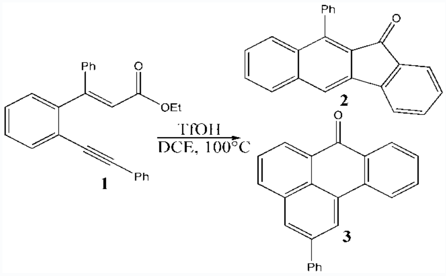
Previous methods to obtain benzo[b]fluorenone include Cu(0)/selectfluor-mediated tandem annulation from 1,6-enynes [21], divergent cycloaromatization reaction of 1,5-enynol and 1,5-diynol [22], iron(III)-catalyzed chemoselective cycloaromatization reaction [23], and cobalt-catalyzed MHP-directed [3 + 2] annulation/ring-opening/dehydration sequence [24]. A great breakthrough was Satyanarayana's TfOH-mediated cascade cyclization of 1,5-enyne. Although desired benzo[b]-fluorenone and benzo[de]anthracen-7-one were obtained, how the triple bond of substrate alkyne was activated by Brønsted acid TfOH? What's detailed process of intramolecular 6-endo-dig cyclization initiated by nucleophilic attack of enoate group? How naphthalene ester intermediate is formed *via* aromatization? Why intramolecular acylation followed by dealcoholation is competitive with retro-Friedel–Crafts C–C cleavage and alternative intramolecular acylation? To solve these questions, it is necessary to conduct in-depth theoretical calculations also focus on function of TfOH.

Computational Details

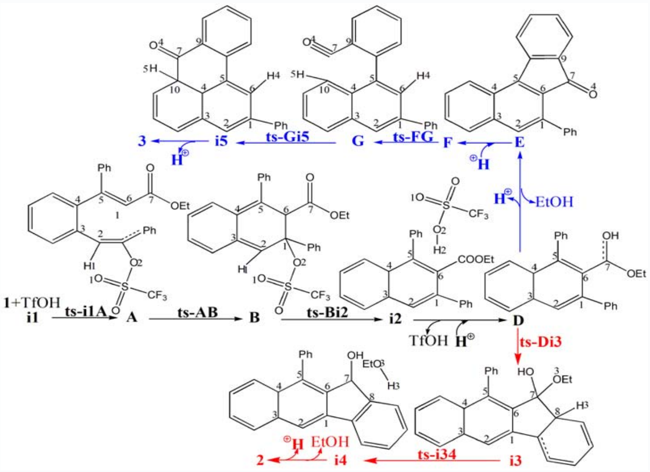
Structures were optimized at M06-2X/6-31G(d) level with GAUSSIAN09 [26]. Among various DFT methods [27], M06-2X functional has smaller deviation between experimental and calculated value than B3LYP hybrid functional [28, 29]. With 6-31G(d) basis set, it can provide best compromise between time consumption 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 373 K and 1 atm in 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 Brønsted acid-mediated cascade cyclization from ethyl (E)-2-(2,3-diphenyl-1H-inden-1-ylidene)acetate 1 to construct benzo[b]-fluorenone 2 and benzo[de]anthracen-7-one 3 (Scheme 1). Shown by Scheme 2, TfOH was selected as Brønsted acid. Under the influence of TfOH, the triple bond of 1 was activated via protonation forming carbocation intermediate A, from which the subsequent 6-endo-dig cyclization results in six-membered ring intermediate B. The naphthalene ester intermediate C is generated via aromatization of B and concomitant recover of TfOH. With sufficient acidic condition, the ester group of C is activated transforming to intermediate D, from which two paths are possible to exist. One aromatic ring undergoes intramolecular acylation followed by dealcoholation producing major product benzofluorenone 2 (red arrow). Alternatively, the intermediate E can be obtained as counterpart of 2 via the same process after removal of EtOH and proton (blue arrow). The protonation of E gives intermediate F, the retro-Friedel–Crafts C–C cleavage of which forms acylium ion intermediate G. A third intramolecular acylation by the third aryl ring from G occurs furnishing another product benzo[de]anthracen-7-one 3 (Scheme1 and 2).



Scheme 1: TfOH-mediated cascade cyclization from ethyl (E)-2-(2,3-diphenyl-1H-inden-1-ylidene)acetate **1** to construct benzo[b]-fluorenone **2** and benzo[de]anthracen-7-one **3**.



Scheme 2: Proposed reaction mechanism of TfOH-mediated cascade cyclization leading to benzo[b]-fluorenone **2** and benzo[de]anthracen-7-one **3** from 1,5-enyne conjugated system **1**. TS is named according to the two intermediates it connects.

Triple Bond Activation/6-endo-dig Cyclization/ Aromatization

Initially, intermediate i1 was obtained between 1 and TfOH as Brønsted acid as starting point (black dash line of Figure 1), from which 1 was protonated by TfOH at alkyne C2 via ts-i1A forming carbocation intermediate A to realize the activation of triple bond. The activation energy is 14.2 kcal mol^{-1} exothermic by -1.2 kcal mol^{-1} in step 1. The transition vector corresponds to noticable proton H1 transfer from O1 of TfOH to C2 and resultant elongation of C2-C1 from triple to double (1.49, 1.2, 1.27 Å) (Figure S1a). Once H1 is bonded to C2, the anion TfO is linked to another alkyne C1 in A.

The subsequent nucleophilic attack takes place via ts-AB with medium activation energy of 23.9 kcal mol^{-1} exothermic by -17.8 kcal mol^{-1} generating complex B in step 2. The transition vector reveals 6-endo-dig cyclization from C1 to C6 and cooperative stretching of C1···C2, C5···C6 from double to single (2.11, 1.4, 1.42 Å) (Figure S1b). This enables formation of six-membered ring intermediate B. However, the concerted path was not located although speculated in experiment. A stepwise process is more advantageous for this 6-endo-dig cyclization under the influence of TfOH.

Then the aromatization of B proceeds via ts-Bi2 with activation energy of 16.3 kcal mol^{-1} exothermic huge by -57.2 kcal mol^{-1} in step 3 leading to i2 binding naphthalene ester intermediate C and recovered TfOH. The proton capture by anion TfO mode is shown

Table 1: The activation energy of all steps.

TS	$\Delta G^{\neq}_{gas}$	$\Delta G^{\neq}_{sol}$
ts-i1A	19.1	14.2
ts-AB	24.6	23.9
ts-Bi2	15.3	16.3
ts-Di3	23.3	15.6
ts-i34	16.8	11.6
ts-FG	5.3	19.9
ts-Gi5	7.5	10.8

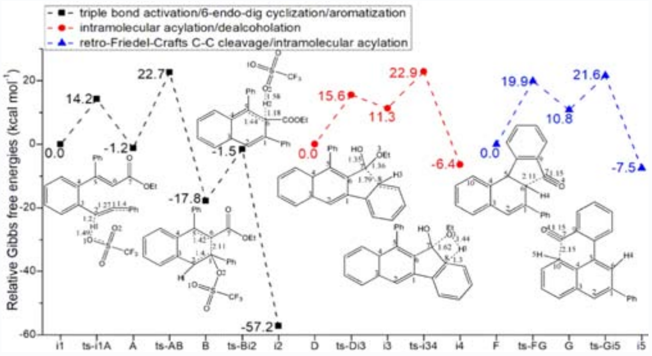


Figure 1: Relative free energy in solvent phase from complex **i1**, **D**, **F**.

by the transition vector including C6···H2···O2 as well as concomitant C5···C6 contracted from single to double (1.18, 1.58, 1.44 Å). After removal of TfOH and an additional proton bonded to ester group, C is activated forming intermediate D as new starting point of following process (Table 1) (Figure 1).

Intramolecular Acylation/Dealcoholation

Two possible paths are considered from D. Via ts-Di3, one aromatic ring undergoes intramolecular acylation involving decreased barrier of 15.6 kcal mol^{-1} and endothermic by 11.3 kcal mol^{-1} in step 4 (red dash line of Figure 1). The transition vector comprises nucleophilic closing of C8 to C7 forming new five membered ring and stretching of C7···O3 as single one (1.79, 1.36 Å) (Figure S1c). The resulting i3 is enolized reactive ready for next step.

The dealcoholation takes place in step 5 via ts-i34 with activation energy of 11.6 kcal mol^{-1} yielding intermediate i4 exothermic by -6.4 kcal mol^{-1}. The transition vector is complex not only illustrating continuous elongation of C7···O3, C8···H3 to breaking down but linkage of O3···H3 as new EtOH molecule (1.62, 1.3, 1.44 Å) (Figure S1d). The major product benzofluorenone 2 is produced once EtOH and proton leaves from stable i4. Undoubtedly, the 6-endo-dig cyclization of step 2 is determined to be rate-limiting for TfOH-mediated cascade reaction from conjugated 1,5-enyne.

Retro-Friedel−Crafts C−C Cleavage/Intramolecular Acylation

Alternatively, via similar intramolecular acylation followed by dealcoholation from a second aromatic ring an intermediate E is also available as counterpart of 2 after removal of EtOH and proton. The protonation on C6 of E gives intermediate F as new starting point of next two steps (blue dash line of Figure 1). The opening of five membered ring occurs from retro-Friedel−Crafts C6-C7 cleavage via ts-FG in step 6 with increased activation energy of 19.9 kcal mol^{-1} endothermic by 10.8 kcal mol^{-1} giving acylium ion intermediate G. The transition vector is about noticable breaking of C6···C7 and cooperative enhanced C7···O4 from double to triple (2.11, 1.15 Å).

At last, a third intramolecular acylation from the third aryl ring of G takes place via ts-Gi5 in step 7 with reduced barrier of 10.8 kcal mol^{-1} exothermic by -7.5 kcal mol^{-1} affording i5. The transition vector reveals C10···C7 linking as single one and restoring of C7···O4 from triple to double (2.15, 1.15 Å) (Figure S1e). This contributes to closure of new six membered ring and carbonyl recovery in i5, from which another product benzo[de]anthracen-7-one 3 is furnished without proton. Two paths are competitive not only from similar barriers but relative energy of counterparts.

Conclusions

The theoretical investigation was provided on Brønsted acid TfOH-mediated cascade cyclization from ethyl (E)-2-(2,3-diphenyl-1H-inden-1-ylidene)acetate. The triple bond was activated via protonation forming carbocation intermediate followed by 6-endo-dig cyclization resulting in six-membered ring. The naphthalene ester intermediate was generated via aromatization and concomitant recover of TfOH. The ester group is activated under acidic condition, from which two paths are competitive not only from similar barriers but relative energy of counterparts. One is intramolecular acylation from the first aromatic ring followed by dealcoholation producing major product benzofluorenone. The alternative from counterpart is via retro-Friedel−Crafts C−C cleavage and subsequent intramolecular acylation by a third aryl ring furnishing another product benzo[de]anthracen-7-one. The 6-endo-dig cyclization is determined to be rate-limiting for TfOH-mediated cascade reaction from conjugated 1,5-enyne.

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 373 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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