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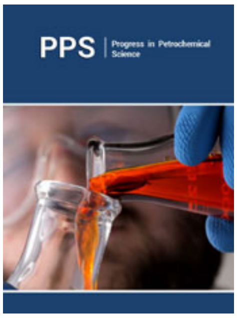

Theoretical Investigation on Cs_2CO_3-Mediated [4+2] Annulation of Ynone and α, α-Dicyanoalkene Leading to Highly Functionalized M-Terphenyl

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Abstract

The first theoretical investigation on Cs_2CO_3-mediated [4+2] annulation of α, α-dicyanoalkene and ynone was provided by our DFT calculation. Via Cs_2CO_3-mediated deprotonation, the α, α-dicyanoalkene is initially converted into vinylogous carbanion from methyl group. Then 4-membered ring carbanion stabilized by two electron-withdrawing cyano groups is generated through nucleophilic attack of methylene on ynone followed by an intramolecular nucleophilic addition. Next the ring opening occurs from strained 4-membered ring. Subsequently the 6-membered ring closure is accomplished via a second intramolecular nucleophilic attack of methylene carbanion to cyano group determined to be rate-limiting for the whole process. Finally, the desired product m-terphenyl is obtained through aromatization of the central ring and afterwards protonation together with recovered Cs_2CO_3.

Keywords: [4+2] annulation; Intramolecular rearrangement; M-terphenyl; Aromatization; Ring opening

Introduction

As a class of aromatic hydrocarbons, terphenyls are characterized by three benzene rings with the terminal one ortho-, meta- or para-substituents relative to the central one. Although p-terphenyl derivatives are natural predominant and recently identified, m-terphenyl derivatives are scarce and has attracted much attention in synthetic chemistry [1]. In addition to exceptional optical and photophysical characteristics [2], a variety of applications have been reported such as laser dyes, OLEDs, textile dye carriers and agents for heat storage, transfer [3]. Furthermore, m-terphenyl moiety displays biological activities in natural compounds [4]. Sawayama reported syntheses of naturally occurring terphenyls [5]. Patrick discovered antiprotozoal activity of dicationic m-terphenyl [6]. Rajakumar found anti-inflammatory activity and toxicity of some novel bis-oxy cyclophane diamides [7]. Samshuddin gave biological evaluation of some functionalized terphenyl derivatives [8]. There is also pharmacological evaluation of m-terphenyl amines as cyclooxygenase inhibitors [9]. New monodentate ruthenium (II) complexes containing terphenyl arenes have cytotoxicity, cellular uptake and DNA interactions stabilizing low-coordinate main-group and transition metals [10]. In synthesis of conjugated polymers, m-terphenyls are employed as smart materials owing to unique optical properties [11]. In the field of synthetic methods, there are reaction of β-cyclo-hexanedione and its ethyl enol ether with phenylmagnesium bromide and two-aryne sequence [12,13].

Adrio discovered aryl cross-coupling reaction using aryl halides to generate central aromatic ring [14]. Shu developed base-mediated synthesis of highly functionalized 2-amino-nicotinonitriles from α-keto vinyl azides and α, α-dicyanoalkenes [15]. Cao reported synthesis of dibenzofurans via benzannulation of 2-nitrobenzofurans and alkylidene malononitriles [16]. Recently, Gopi realized one-pot regioselective synthesis of meta-terphenyls via [3+3] annulation of nitro-allylic acetates with alkylidene-malononitriles [17]. Then Davas published divergent approach to highly substituted arenes via [3+3] annulation of vinyl sulfoxonium ylides with ynones [18]. Similar progresses are Tf2O-induced selective 1, 3-transposition/cyclization of ynones and sequential condensation/bi-annulation reactions of β-(2-aminophenyl)-α, β-ynones with 1, 3-dicarbonyls [19,20]. Clarke realized atom and step economic synthesis of functionalized piperidines using five-component condensation [21]. Wang gave cerium ammonium nitrate-catalyzed multicomponent reaction for efficient synthesis of functionalized tetrahydropyridines [22].

The mechanism of this annulation was researched in synthesis of bridged ring system initiated by ring expansion of indene-1,3-dione and $AgNO_3$-catalysed intramolecular cyclization to access cyclopentanones and spiro-cyclopentanones [23,24]. Another breakthrough was Cs_2CO_3-catalyzed [4+2] annulation of ynone and α, α-dicyanoalkene [25]. Although desired m-Terphenyl was synthesized, how intramolecular rearrangement followed by ring cyclization was achieved for the whole process? What's the function of Cs_2CO_3 in base-mediated deprotonation converting α, α-dicyanoalkene into vinylogous carbanion? How 4-membered ring carbanion and 6-membered intermediate were obtained via ring opening in consecutive mode? How Cs_2CO_3 is recovered along with final aromatization of central ring?

Computational Details

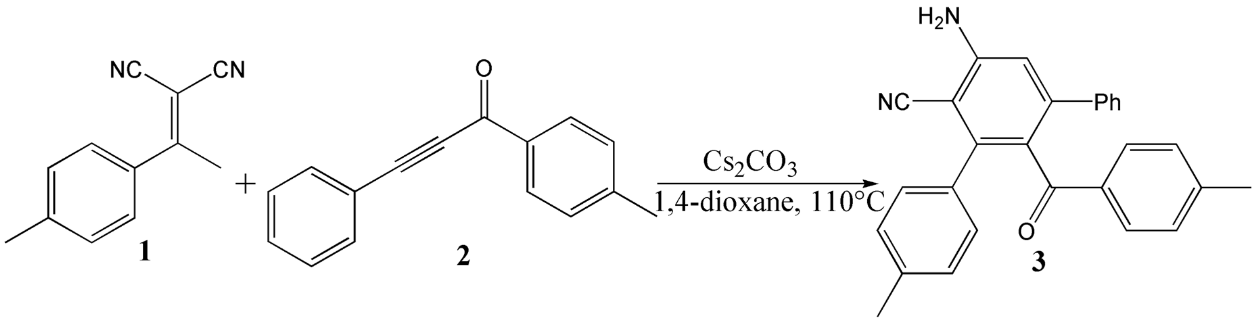
The geometry optimizations were performed at the B3LYP/BSI level with the Gaussian 09 package [26,27]. The mixed basis set of LanL2DZ for Cs and 6-31G(d) for other non-metal atoms [28-32] was denoted as BSI. Different singlet and multiplet states were clarified with B3LYP and ROB3LYP approaches including 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 383K and 1atm for each structure in 1, 4-dioxane. The solvation-corrected free energies were obtained at the B3LYP/6-311++G (d, p) (LanL2DZ for Cs) 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).

Results and Discussion

The mechanism was explored for Cs_2CO_3-mediated [4+2] annulation of α, α-dicyanoalkene 1 and ynone 2 leading to m terphenyl 3 (Scheme 1). As is illustrated by black arrow of Scheme 2, first, via Cs_2CO_3-mediated deprotonation, α, α-dicyanoalkene 1 is converted into vinylogous carbanion A from methyl group of 1. Then, the nucleophilic attack of A on ynone 2 leads to intermediate B followed by an intramolecular nucleophilic addition forming 4-membered ring carbanion intermediate C stabilized by two electron-withdrawing cyano groups. Next, the ring opening of C occurs from strained 4-membered ring giving intermediate D, which turns into E through another intramolecular nucleophilic attack of methyl carbanion to cyano group. Finally, the desired product m-terphenyl 3 is achieved through aromatization of the central ring from E and protonation afterwards along with recovery of Cs_2CO_3. Figure 1 listed schematic structures of optimized TSs in Scheme 2. Table 1 gave activation energy for all steps.

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	11.4	12.6
ts-i3B	13.3	14.9
ts-BC	0.3	0.6
ts-CD	18.5	17.6
ts-DE	26.8	24.5
ts-Ei4	21.9	20.4
ts-i56	1.0	3.4



Scheme 1: Cs_2CO_3-mediated [4+2] annulation of α, α-dicyanoalkene 1 and ynone 2 leading to functionalized m-terphenyl 3.

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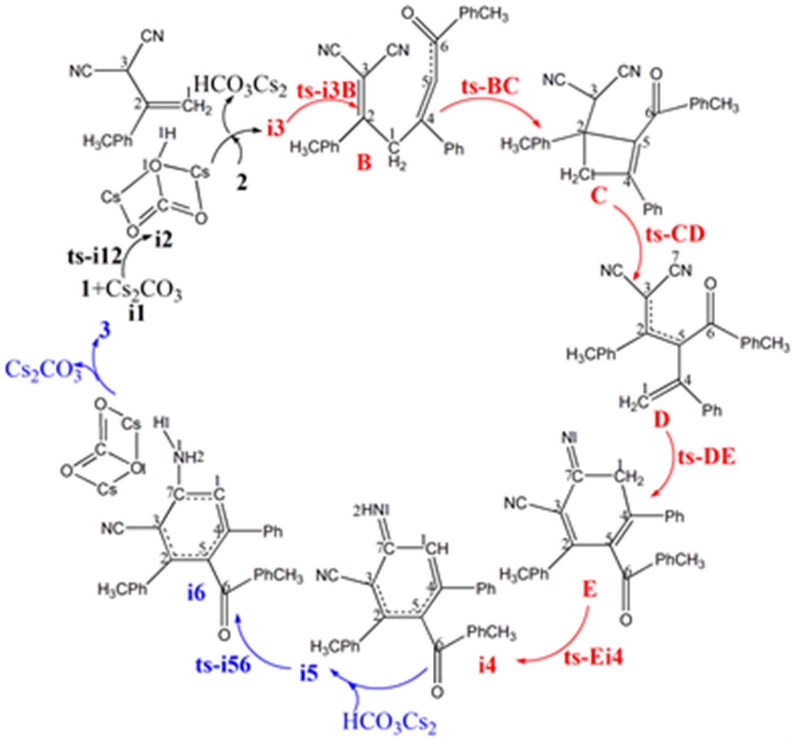

Scheme 2: Proposed reaction mechanism of Cs_2CO_3-mediated [4+2] annulation of 1 and 2 to access 3. TS is named according to the two intermediates it connects.

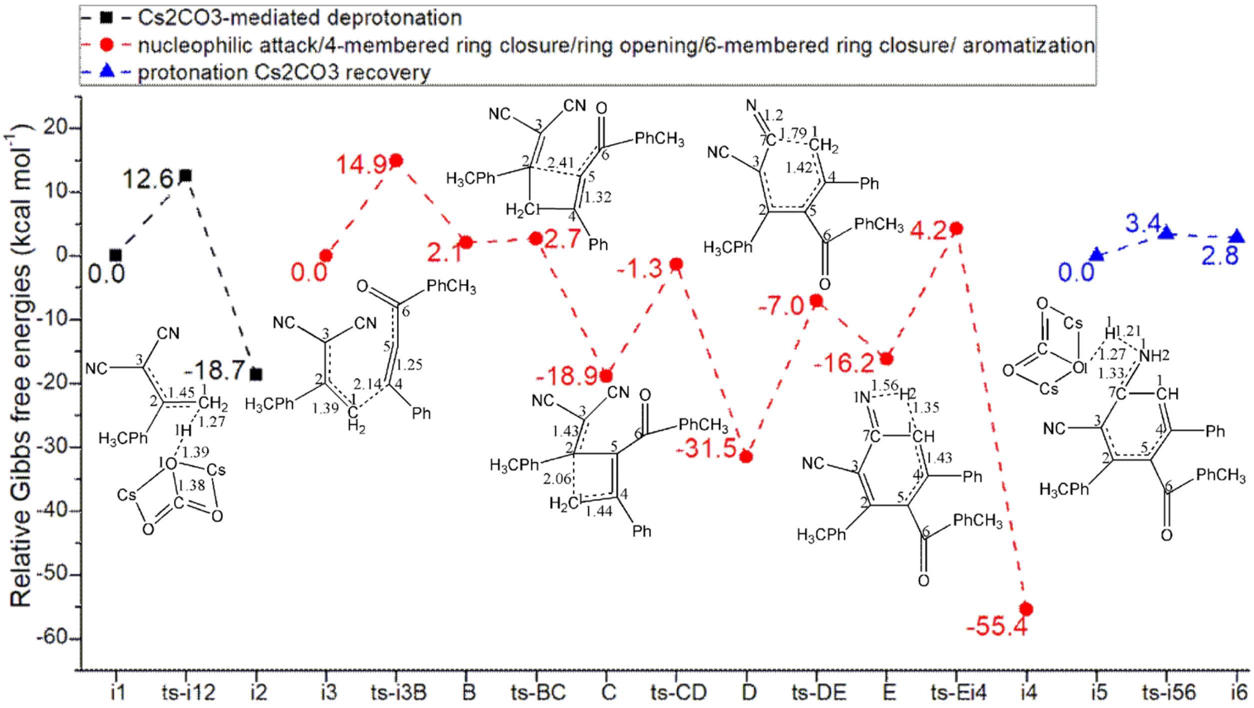

Figure 1: Relative Gibbs free energy profile in solvent phase starting from complex i1, i3, i5 (Bond lengths of optimized TSs in Å).

Cs_2CO_3-mediated deprotonation

In step 1, α, α-dicyanoalkene 1 and Cs_2CO_3 forms intermediate i1, from which the deprotonation occurs via ts-i12 with the activation energy of 12.6kcal mol^{-1} exothermic by -18.7kcal mol^{-1} producing vinylogous carbanion A (black dash line of Figure 1). The transition vector corresponds to proton H1 on methyl group captured by carbonyl of Cs_2CO_3 denoted as C1⋯H1⋯O1 (1.27, 1.39 Å) (Figure S1a). Along with the shortening of C1-C2 from single bond to double (1.45 Å), methyl is converted into methylene in A, which is reactive and ready to initiate next step.

Nucleophilic attack/4-membered ring closure/ring opening/6-membered ring closure

Then, the intermediate i3 binding A and ynone 2 is taken as new starting point of next five steps (red dash line of Figure 1). The nucleophilic attack of A to 2 leads to intermediate B via ts-i3B with activation energy of 14.9kcal mol^{-1} endothermic by 2.1kcal mol^{-1} in step 2. The transition vector not only includes C1 bonding with terminal alkyne C4 but resultant elongation of C1-C2 from double to single and C4-C5 from triple to double (2.14, 1.39, 1.25 Å). Thus, complex B is obtained with typical C1-C4 single bond. Subsequently, an intramolecular nucleophilic addition takes place to accomplish 4-membered ring closure via ts-BC in step 3 with low activation energy of 0.6kcal mol^{-1} exothermic by -18.9kcal mol^{-1} delivering carbanion intermediate C. From detailed atomic motion of transition vector, the negative alkyne C5 is approaching C2 together with assisted elongation of C2-C3 and C6-C5 from double to single (2.41 Å) (Figure S1b). Once the 4-membered ring is closed involving C5-C2 single bond, negative charge is transferred at C3 stabilized by two electron-withdrawing cyano groups. Next, from strained 4-membered ring, the ring opening of C is readily via ts-CD in step 4 with activation energy of 17.6kcal mol^{-1} exothermic by -31.5kcal mol^{-1} affording intermediate D. The transition vector suggests facile cleavage of C1···C2 single bond driven by enhanced C3-C2 and C1-C4 from single to double (2.06, 1.43, 1.44 Å) (Figure S1c).

Clearly, the much more stable of D compared with C is expected as a result of ring tension release. The negative charge is located at methylene C1 in D. Another intramolecular nucleophilic attack through methylene carbanion to cyano group happens via ts-DE with increased activation energy of 24.5kcal mol-1 exothermic by -16.2kcal mol^{-1}. D turns into E realizing 6-membered ring closure in step 5. The transition vector contains linkage of C1···C7 as well as stretching of C1···C4 from double to single and C7···N1 from triple to double (1.79, 1.42, 1.2 Å) (Figure S1d). The 6-membered ring is yielded with typical C1-C7 single bond in E.

Aromatization/protonation- Cs_2CO_3 recovery

Then in step 6, the central ring of E undergoes aromatization via ts-Ei4 with reduced activation energy of 20.4kcal mol^{-1} exothermic by -55.4kcal mol^{-1} yielding intermediate i4. The transition vector suggests apparent proton donation by methylene C1 to imine N1 through transfer mode C1···H2···N1 and concerted shortening of C1-C4 from single bond to double (1.35, 1.56, 1.43 Å) (Figure S1e). The preliminarily protonation is realized via this step effectively pull the entire process with huge released energy. On the basis of previous step, the product m-terphenyl 3 is finally achieved through afterwards proton transfer in step 7 (blue dash line of Figure 1). The transition vector reveals proton H1 provided by O1 of HCO_3Cs_2 to N1 via O1···H1···N1 along with of slight elongation of N1-C7 (1.27, 1.21, 1.33 Å) (Figure S1f). The last step happens via ts-i56 with small barrier of 3.4kcal mol^{-1} endothermic by 2.8kcal mol^{-1} giving i6, from which the catalyst Cs_2CO_3 is simultaneously recovered. Comparatively, the 6-membered ring closure of step 5 is determined to be rate-limiting for Cs_2CO_3-mediated [4+2] annulation producing m terphenyl.

Conclusion

In summary, the first theoretical investigation was provided by our DFT calculation on Cs_2CO_3-mediated [4+2] annulation of α, α-dicyanoalkene and ynone. The α, α-dicyanoalkene is initially converted into vinylogous carbanion from methyl group via Cs_2CO_3-mediated deprotonation. Then, the nucleophilic attack of methylene on ynone followed by an intramolecular nucleophilic addition leads to 4-membered ring carbanion stabilized by two electron-withdrawing cyano groups. Next, the ring opening occurs from strained 4-membered ring. Subsequently, the second intramolecular nucleophilic attack of methylene carbanion to cyano group accomplishes 6-membered ring closure determined to be rate-limiting for the whole process. Finally, the desired product m-terphenyl is obtained through aromatization of the central ring and afterwards protonation assisted by Cs_2CO_3 recovery.

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 383K].

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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