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Article

Annulation of Internal Alkyne toward Synthesis of Selective *E*-Benzofulvene and Mechanistic Study using Density Function Theory Calculation

Shubhendu Dhara[1]*, Anuvab Das[2], Dhiraj Das[3], Rajesh Koner[1]

[1]Department of Chemistry, Bhairab Ganguly College, Belgharia, Kolkata, West Bengal, India, [2]Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California, [3]Department of Chemistry, University of Calcutta, Kolkata, West Bengal, India

ABSTRACT

An efficient approach has been devised for the synthesis of highly functionalized *E*-benzofulvenes. While annulating an internal alkyne with 4-(2-bromophenyl)but-3-en-2-one yielded up to 87% of E-benzofulvene derivatives. Double functionalization of C_{sp2}-H and *ortho*-C-Br bonds in an *α,β*-unsaturated arylketone in the presence of cheap catalyst $PdCl_2$ with alkyne triple bond afforded almost quantitative formation of highly substituted benzofulvene in N,N-dimethylformamide solvent and under reasonable reaction conditions. Detail mechanism of annulations of alkynes to give selective *E*-benzofulvenes has been studied by density function theory analysis using the Gaussian 09 program.

Key words: *E*-Benzofulvene, Annulation, Internal alkyne, Wittig reaction, *o*-bromostyrene, Density function theory.

1. INTRODUCTION

Benzofulvene core is indeed privileged scaffolds, found in numerous drug candidates with exceptional biological activities (Figure 1) [1]. Apart from this, they also have applications in material science and polymer-based drug delivery systems [2]. Moreover, benzofulvene moiety is also useful in synthesizing organometallic complexes exhibiting excellent catalytic activity [3]. Because of their ubiquity, it has become the need of the hour to find out efficient synthetic methods to benzofulvene moiety.

In 1900, Thiele [4a] first reported the synthesis fulvene through alkoxide-mediated condensation of ketones and cyclopentadiene with poor yields due to competing aldol reactions. Since then, many scientists have developed various new strategies to synthesize this potential core structural unit, such as reactions involving transition metal catalyzed cyclization of 1,3-diene derivatives of Morita-Baylis-Hillman adduct [4b], radical cyclization of enedynes [4c], and many more. Silver-mediated Nazarov-type cyclization has been reported by Cordier *et al.* to benzofulvenes [5a]. Hua *et al.* reported synthesis of benzofulvene through Pd(II)-catalyzed alkyne-directed C(sp2)-H bond activation [5b].

The formation of C-C bond through C-H functionalization reactions [6] is of great importance in modern synthetic organic chemistry. This is mainly because of its' advantage of low cost and waste reduction, and it eliminates the need for prior functionalization of the substrate and thus reduces the number of steps in the overall reaction. Chinnagolla and Jeganmohan [7] developed a strategy for synthesis of substituted indenols and benzofulvenes by ruthenium catalyzed regioselective cyclization of aromatic ketones with alkynes. An iridium catalyzed synthesis of benzofulvenes has been described by Shibata *et al.* [8]. Although these aforesaid and many other literature reports have generated good yields of benzofulvene, most of the reports used costly catalysts, additives, and drastic reaction conditions. The structural diversities of benzofulvene core always demand development of new and efficient methods of synthesis.

In the course of our ongoing research on developing new synthetic methodologies for promising core structural unit, we have developed a diverse strategy for selective *E*-benzofulvenes using palladium catalyzed coupling of *o*-bromostyrene and internal alkyne.

2. EXPERIMENTAL

2.1. General

High-quality reagents were purchased from Sigma-Aldrich. Analytical grade commercial reagents and solvents were purified by standard procedures before use. Chromatographic purification was done with 60–120 mesh SiO_2 gel (Merck). For reaction monitoring, pre-coated SiO_2 gel 60 F254 sheets (Merck) were used. ^{1}H-NMR (600 MHz and 200 MHz) spectra were recorded on BRUCKER-AC 600 MHz and BRUCKER-AC 200 MHz spectrometer, respectively. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: Chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, and dd = double doublet), and coupling constant (Hz). ^{13}C-NMR (150 MHz and 50 MHz) spectra were recorded on BRUCKER-AC 600 MHz and BRUKER-AC 200 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 77.23 ppm). HRMS (ESI) spectra were taken using Waters Xevo G2 QTof mass

***Corresponding author:**
E-mail: dharashubhednu@gmail.com

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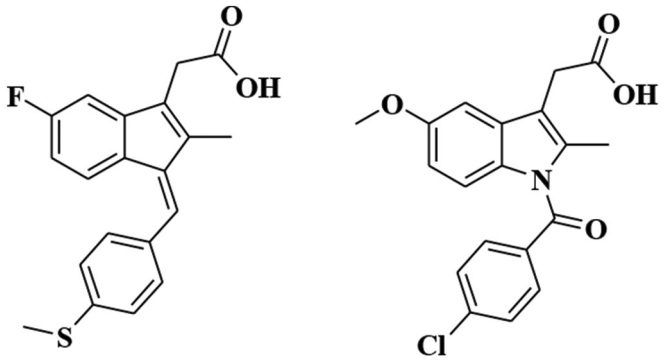


Sulindac sulfide **Inomethacin**

Figure 1: Bioactive benzofulvenes.

spectrometer. Melting points of the final compounds were checked after recrystallization from ethanol.

2.2. Synthesis of Precursors

Precursor *o*-bromostyrenes **2a-i** were synthesized using Wittig and Schöllkopf [9] reaction from the corresponding 2-bromovinylaldehydes. While reacting with substituted 2-bromovinylaldehydes in dry DCM at room temperature, 1-(triphenylphosphoranylidene)propan-2-one gave quantitative formation of *o*-bromostyrenes **2a-i** (Figure 2).

2.3. General Procedure for the Preparation Substrates ortho-Bromophenylbutenones (2a-i)

In a 25 mL round bottomed flask, *o*-bromobenzaldehyde (1 mmol) and 1-(triphenylphosphoranylidene)propan-2-one (3 mmol) were taken under argon atmosphere and 3 mL of dry DCM was added to it. Then, the mixture was stirred for 3–4 h at rt. The completion of the reaction was determined by thin-layer chromatography (TLC). Solvent evaporated under reduced pressure and the desired product was isolated by column chromatography and mixture of ethyl acetate: petroleum ether (1:10) used as eluents. All the precursors are identified by analysis of respective elemental and spectral data. Spectral data of the representative compounds are reported here.

2.2.1. (E)-4-(2-Bromophenyl)but-3-en-2-one (2a)

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.90 (d, *J* = 16.3 Hz, 1H), 7.62 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.38–7.20 (m, 2H), 6.63 (d, *J* = 16.3 Hz, 1H), 2.43 (s, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 199.98, 149.76, 141.20, 131.23, 129.48, 128.47, 127.66, 126.79, 120.79, 32.34; elemental analysis: C, 53.36; H, 4.03 %; found: C, 53.30; H, 4.00%.

2.2.2. (E)-4-(2-bromo-5-fluorophenyl)but-3-en-2-one (2b)

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 16.3 Hz, 1H), 7.60 (dd, *J* = 8.8, 5.3 Hz, 1H), 7.34 (dd, *J* = 9.4, 2.9 Hz, 1H), 7.01 (td, *J* = 8.7, 8.3, 2.9 Hz, 1H), 6.62 (d, *J* = 16.2 Hz, 1H), 2.45 (s, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 197.96, 164.58, 159.66, 140.81, 134.90, 130.69, 119.83, 118.84, 114.60, 27.65. Elemental analysis: C, 49.41; H, 3.32 %; found: C, 49.36; H, 3.22 %; require HRMS (ESI) m/z of $C_{10}H_9BrFO^+$ $[M+H]^+$: 242.9821; observed value: 242.9810.

2.2.3. (E)-4-(2-bromo-4,5-dimethoxyphenyl)but-3-en-2-one (2e)

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 16.2 Hz, 1H), 6.98 (d, *J* = 6.8 Hz, 2H), 6.45 (d, *J* = 16.2 Hz, 1H), 3.83 (s, 6H), 2.33 (s, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 198.22, 151.40, 148.59, 141.69, 127.56, 125.99, 117.48, 115.42, 108.94, 56.16, 55.96, 26.91; elemental analysis: C, 50.55; H, 4.60%; found: C, 50.50; H, 4.52%; require HRMS (ESI) m/z of $C_{12}H_{14}BrO3^+$ $[M+H]^+$: 285.0126; observed value: 285.0120.

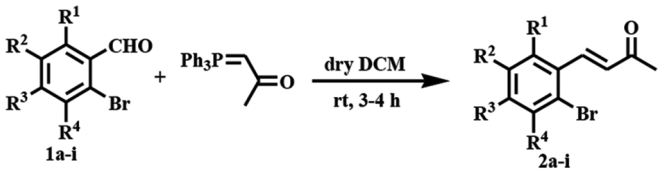


Figure 2: Synthesis of precursors.

2.4. Synthesis of Benzofulvenes

Internal alkynes first undergoes cross-coupling with C-Br bond of *o*-bromostyrenes and followed by C-C bond formation. On reacting 4-(2-bromophenyl)but-3-en-2-one (**2a**) with diphenylacetylene (**4**) in the presence of Pd-catalyst and base, it undergoes an annulation of alkyne to afford the benzofulvene **3a** in good yield (Figure 3).

The formation of benzofulvene was determined by ^{1}H- and ^{13}C-NMR and IR spectroscopic measurement. Stereoselective formation of *E*-isomer was determined by NOESY and COSY correlation NMR spectroscopy. The structure of stereoisomeric *E*-benzofulvene was unequivocally confirmed by X-ray single crystal analysis. Figure 4 shows the X-ray crystal structures of **3e** and **3g** having CCDC no. 1059440 and 1059441, respectively. The above result prompted us to find out the best set of reaction conditions for generation of benzofulvenes. We began our investigation with 4-(2-bromophenyl) but-3-en-2-one (**2a**) and diphenylacetylene (**4**) as the model substrates. Several influential factors were taken into consideration such as catalyst, ligand, base, solvent, and temperature in the reaction. The study revealed that $Pd(OAc)_2$ was inefficient to give any substantial yield of benzofulvene leaving behind only unreacted starting materials. Moreover, the $Pd(PPh_3)_4$ and other Pd(0) catalysts gave very poor yields of benzofulvene. The $PdCl_2$ was the most effective catalyst in our reaction.

Among the various organic and inorganic bases that we tried, NaOAc proved its superiority over others. We then examined the effect of different polar and non-polar solvents and N,N-dimethylformamide (DMF) was observed to give the highest reaction yield. Initially, the reaction mixture was heated to 80°C in the presence of $Pd(OAc)_2$ and Cs_2CO_3 which yielded no benzofulvene even after 12 h. Elevation of reaction temperature to 100°C with concomitant change of base to NaOAc gave 15% benzofulvene. Highest increment of product formation was seen while changing the catalyst to $PdCl_2$ in combination with PPh_3 as added ligand with 85% of yield of benzofulvene and reducing the reaction time to 3 h. After rigorous screening, we finalized the set of optimal reaction conditions to be $PdCl_2$ (5 mol%) as the catalyst along with PPh_3 (0.2 mmol) as ligand in the presence of NaOAc (1.5 mmol) as base in DMF solvent and at 100°C temperature within 3 h (Table 1, entry 10).

Now with the optimized reaction conditions at our disposal, we tried to establish the general scope and applicability of our method by synthesizing various substituted benzofulvenes **3a-g,** as illustrated in Table 2. Results in the table reflect the effect of electron-donating and electron-withdrawing substituents in the substrate on the product yields. It clearly demonstrates that electron-withdrawing groups such as F and NO_2 resulted relatively lower yield of benzofulvene (**3b, 3d**). Most probable reason would be the lower reactivity of the double bond in the carbopalladation step during 5-*exo-trig* cyclization. In contrast, electron-donating groups OMe, Me afforded higher amount of benzofulvenes (**3c, 3e**). Again, the presence of three OMe groups gave only 62% of benzofulvene **3f** which may be due destabilization of the product arising from steric interaction between the adjacent OMe and phenyl ring in the product. Interestingly, our method well tolerates the naphthalenoid and hetero-naphthalenoid substituted substrates with subsequent formation the corresponding products.

2.5. General Procedure for the Annulation Reaction

In a 25 mL round bottomed flask, 4-(2-bromophenyl)but-3-en-2-one (**2a**) (0.5 mmol) and diphenylacetylene (0.5 mmol), $PdCl_2$ (5 mol%), PPh_3 (0.2 mmol), NaOAc (1.5 mmol), and dry DMF (3 mL) were taken in argon atmosphere. The mixture was degasified for 10 min and heated to 100°C temperatures for 3 h. The completion of the reaction was determined by TLC. Solvent evaporated under reduced pressure and the desired product was isolated by column chromatography and mixture of ethyl acetate: petroleum ether (1:20) as eluents. The formation of benzofulvene was determined by ^{1}H- and ^{13}C-NMR and IR spectroscopic measurement. Spectroscopic data are presented herewith.

2.5.1. (E)-1-(2,3-Diphenyl-1H-inden-1-ylidene)propan-2-one (3a)
Red solid; m.p:158–160°C; yield: 85%; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.54 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.36–7.25 (m, 11H), 7.19 (dd, *J* = 7.7, 1.7 Hz, 2H), 6.49 (s, 1H), 2.39 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.75, 149.52, 145.71, 144.18, 139.41, 134.03, 133.85, 133.28, 130.99, 130.09, 129.24, 128.22, 128.18 (2C), 128.17, 127.87 (2C), 127.50 (2C), 127.43, 127.37, 126.55, 120.55, 32.11; elemental analysis: C, 89.41%; H, 5.63%; found: C, 89.35%; H, 5.60%.

Table 1: Determination of the optimal conditions[a,b].

Entry	Catalyst	Base	Solvent	Temp (°C)	Time (h)	Yield (%)
1	Pd(OAc)2	Cs2CO3	DMF	80	12	-
2	Pd(OAc)2	K2CO3	DMF	80	12	-
3	Pd(OAc)2	K2CO3	DMF	100	12	Trace
4	Pd(OAc)2	Na2CO3	DMF	100	12	Trace
5	Pd(OAc)2	NaOAc	DMF	100	12	15
6	Pd(OAc)2	Et3N	DMF	100	12	Trace
7	Pd(PPh3)4	NaOAc	DMF	100	8	44
8	Pd(PPh3)4	tBuOK	DMF	100	8	-
9	Pd2(dba)3	NaOAc	DMF	100	8	35
10	PdCl2	NaOAc	DMF	100	3	85
11	PdCl2	NaOAc	Toluene	100	3	62
12	PdCl2	NaOAc	DMSO	100	3	60
13	PdCl2	NaOAc	H2O	100	3	50
14	PdCl2	NaOAc	DMF	120	3	85
15	PdCl2	NaOAc	DMA	100	3	68

[a]Reagents and conditions: 2a (0.5 mmol), diphenylacetylene (0.5 mmol), Pd-catalyst (5 mol%), PPh3 (0.2 mmol), base (1.5 mmol), solvent (3 mL), 80–100°C, 3–12 h. [b]Isolated yields. DMF: N,N-Dimethylformamide

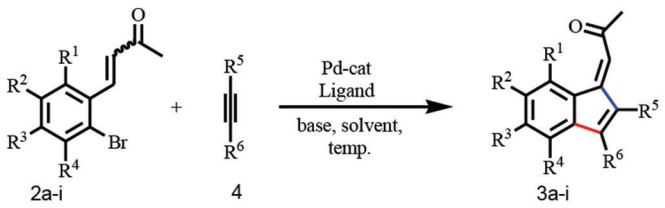


Figure 3: Annulation of internal alkyne.

2.5.2. (E)-1-(6-Fluoro-2,3-diphenyl-1H-inden-1-ylidene)propan-2-one (3b)
Red solid; m.p:172–174°C; yield: 69%; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.39 (dd, *J* = 10.1, 2.5 Hz, 1H), 7.36–7.28 (m, 6H), 7.25–7.22 (m, 2H), 7.21 (dd, *J* = 8.2, 5.2 Hz, 1H), 7.18–7.15 (m, 2H), 7.01 (td, *J* = 8.5, 2.5 Hz, 1H), 6.51 (s, 1H), 2.38 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.35, 163.69, 162.07, 148.97, 145.32, 140.05, 139.15, 135.12, 133.70, 130.92 (2C), 129.13 (2C), 128.29 (2C), 128.25, 128.05, 127.98, 127.52, 121.00, 116.02, 115.87, 115.01, 29.71; found: 341.1340; elemental analysis: C, 84.68%; H, 5.03 %; found: C, 84.60%; H, 5.00%; require HRMS (ESI) m/z of $C_{24}H_{18}FO^+$ $[M+H]^+$: 341.1342; observed value: 341.1339.

2.5.3. (E)-1-(6-Methyl-2,3-diphenyl-1H-inden-1-ylidene)propan-2-one (3c)
Red solid; m.p:180–182°C; yield: 87%; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.50 (dd, *J* = 7.7, 3.4 Hz, 1H), 7.36–7.36 (m, 6H), 7.30–7.26 (m, 2H), 7.20 (d, *J* = 7.4 Hz, 2H), 7.12 (d, *J* = 7.4 Hz, 2H), 6.47 (d, *J* = 2.3 Hz, 1H), 2.40 (s, 3H), 2.39 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.58, 149.78, 145.77, 144.61, 140.57, 139.88, 134.15, 134.01, 131.01, 130.70, 129.29, 128.25(2C), 128.17, 127.84 (3C), 127.80 (2C), 127.40, 126.69, 126.58, 121.62, 32.17, 21.88; elemental analysis: C, 89.25%; H, 5.99%; found: C, 89.21%; H, 5.90%; require HRMS (ESI) m/z of $C_{25}H_{21}O^+$ $[M+H]^+$: 337.1592; found: 337.2004.

2.5.4. (E)-1-(6-Nitro-2,3-diphenyl-1H-inden-1-ylidene)propan-2-one (3d)
Red solid; m.p:176–178°C; yield: 73%; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 9.42 (d, *J* = 2.1 Hz, 1H), 8.27 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.39–7.37 (m, 3H), 7.35 (dd, *J* = 5.2, 1.9 Hz, 3H), 7.25–7.23 (m, 2H), 7.19 (dd, *J* = 6.6, 2.9 Hz, 2H), 6.64 (s, 1H), 2.44 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.13, 149.83, 147.38, 147.32, 144.50, 144.15, 133.78, 132.91, 132.72, 130.71, 130.14, 129.13, 128.60 (2C), 128.55, 128.50(2C), 128.45 (2C), 128.16, 125.95, 121.96, 120.22, 32.17; elemental analysis: C, 78.46%; H, 4.66%; N, 3.81%; found: C, 78.40%; H, 4.63%; N, 3.76%; required HRMS (ESI) m/z of $C_{24}H_{18}NO_3^+$ $[M+H]^+$: 368.1287; found: 368.1271.

2.5.5. (E)-1-(5,6-Dimethoxy-2,3-diphenyl-1H-inden-1-ylidene) propan-2-one (3e)
Reddish brown solid; m.p:198–200°C; yield: 80%; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.57 (s, 1H), 7.36–7.27 (m, 6H), 7.25 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.16 (dd, *J* = 7.8, 1.7 Hz, 2H), 6.82 (s, 1H), 6.44 (s, 1H), 4.04 (s, 3H), 3.89 (s, 3H), 2.37 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.42, 150.98, 150.54, 148.00, 145.66, 138.60, 138.39, 134.13,

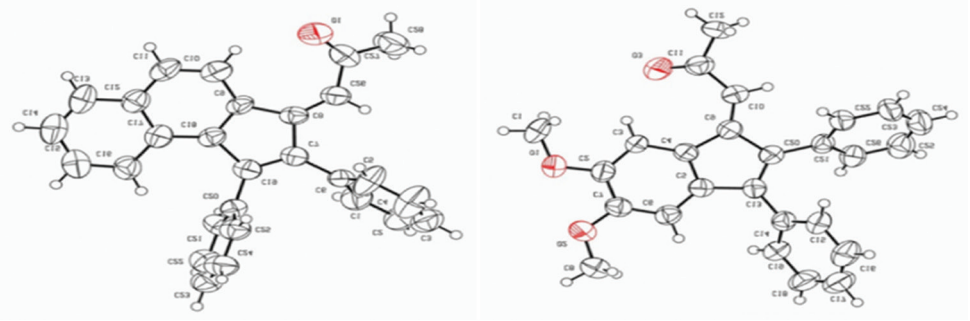
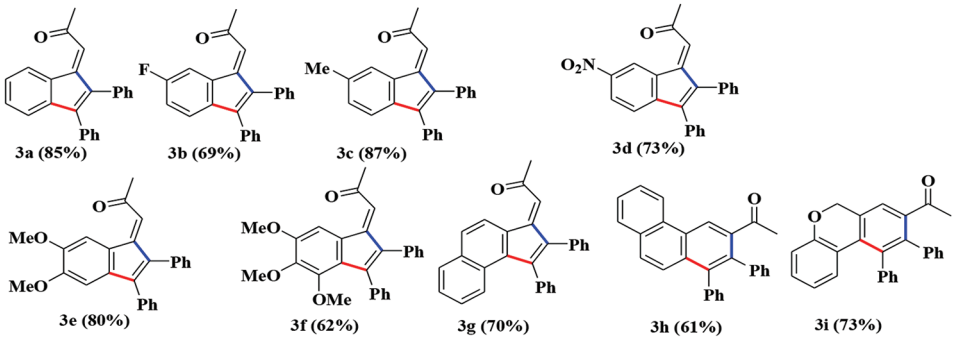


Figure 4: ORTEP view of **3e** and **3g.**

Table 2: Synthesis of *E*-benzofulvenes[a,b].



[a]Reagents and conditions: **2a-i** (0.5 mmol), diphenylacetylene (0.5 mmol), $PdCl_2$ (5 mol%), PPh_3 (0.2 mmol), NaOAc (1.5 mmol), DMF (3 mL), 100oC, 3 h. [b]Isolated yields in the parenthesis PhPhO

134.03, 131.07, 129.12 (2C), 128.33 (2C), 128.13 (2C), 127.88 (2C), 127.27, 125.85, 125.74, 112.00, 104.74, 56.29, 56.12, 32.39; elemental analysis: C, 81.65%; H, 5.80%; found: C, 81.60%; H, 5.75%; required HRMS (ESI) m/z of $C_{26}H_{23}O_3^+$ $[M+H]^+$: 383.1647; found: 383.1650.

2.5.6. (E)-1-(4,5,6-Trimethoxy-2,3-diphenyl-1H-inden-1-ylidene) propan-2-one (3f)

Red solid; m.p:216–218°C; yield: 62%; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.29–7.22 (m, 8H), 7.10 (d, *J* = 6.8 Hz, 2H), 6.43 (s, 1H), 4.01 (s, 3H), 3.91 (s, 3H), 3.31 (s, 3H), 2.36 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 199.40, 153.01, 150.72, 148.32, 146.38, 144.82, 139.00, 135.48, 133.92, 131.13, 129.51, 129.37, 127.92, 127.87 (2C), 127.20 (2C), 127.14 (2C), 127.09 (2C), 126.30, 108.89, 61.14, 61.10, 56.39, 32.42; elemental analysis: C, 78.62%; H, 5.86%; found: C, 78.59%; H, 5.81%; required HRMS (ESI) m/z of $C_{27}H_{25}O_4^+$ $[M+H]^+$: 413.1753; found: 413.1749.

2.5.7. (E)-1-(1,2-Diphenyl-3H-cyclopenta[a]naphthalen-3-ylidene) propan-2-one (3g)

Dark brown solid; m.p:190–192°C; yield: 70%; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.47 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.42–7.27 (m, 10H), 7.19 (dt, *J* = 7.7, 1.5 Hz, 2H), 7.15–7.11 (m, 1H), 6.59 (d, *J* = 1.5 Hz, 1H), 2.47 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 200.76, 148.40, 146.90, 140.59, 140.31, 137.07, 135.75, 133.78, 131.12 (2C), 130.34, 130.30, 129.59 (2C), 128.65, 128.24 (2C), 127.94, 127.85, 127.69 (2C), 127.33, 127.20, 125.94, 125.59, 124.94, 122.95, 32.04; elemental analysis: C, 90.29%; H, 5.41%; found: C, 90.27%; H, 5.33%; required HRMS (ESI) m/z of $C_{28}H_{21}O^+$ $[M+H]^+$: 373.1592; found: 373.1595.

2.5.8. 1-(1,2-Diphenylphenanthren-3-yl)ethanone (3h)

Red sticky liquid; yield: 61%; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 9.36 (s, 1H), 8.86 (d, *J* = 8.4 Hz, 1H), 7.99 (dd, *J* = 21.9, 8.3 Hz, 2H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.67 (ddd, *J* = 34.7, 15.1, 7.7 Hz, 4H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 6.9 Hz, 1H), 7.31 (dd, *J* = 18.2, 11.0 Hz, 3H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.12 (d, *J* = 9.1 Hz, 1H), 2.92 (s, 3H).; ^{13}C-NMR (150 MHz, $CDCl_3$): δ 205.73, 141.35, 135.23, 134.10, 133.79, 133.40, 133.39, 132.80, 132.08, 130.47, 130.06, 129.73, 129.27, 128.99 (2C), 128.97, 128.46, 127.73, 127.69, 126.66, 126.17 (2C), 126.16, 125.42, 125.12, 124.64, 122.62, 31.29; elemental analysis: C, 90.29%; H, 5.41%; found: C, 90.21%; H, 5.36%; required HRMS (ESI) m/z of $C_{28}H_{21}O^+$ $[M+H]^+$: 373.1592; found: 373.1587.

Table 3: Crystallographic data.

Compound	3e	3g
Formula	$C_{26}H_{22}O_3$ CCDC-1059440	$C_{28}H_{20}O_1$ CCDC-1059441
Mg mol^{-1}	382.44	372.44
Space group	$P_2(1)/n$	P−1
Lattice system	Monoclinic	Triclinic
a/Å	11.124(4)	9.801(7)
b/Å	12.744(5)	10.642(8)
c/Å	14.913(5)	10.996(8)
α/deg	90.00	73.16(3)
β/deg	95.486(12)	67.94(2)
γ/deg	90.00	79.96(3)
V/$Å^3$	2104.5(13)	1014.5(13)

2.5.9. 1-(9,10-diphenyl-6H-benzo[c]chromen-8-yl)ethanone (3i)

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.62 (dd, *J* = 15.9, 9.2 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.50–7.36 (m, 3H), 7.32–7.19 (m, 2H), 7.15 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.06–7.00 (m, 2H), 6.90 (d, *J* = 7.2 Hz, 2H), 4.99 (s, 2H), 2.42 (s, 3H); ^{13}C-NMR (151 MHz, $CDCl_3$) δ 210.11, 148.80, 148.07, 147.08, 146.41, 138.53, 138.47, 137.32, 135.45, 130.23, 128.11, 127.10, 126.64, 126.35, 126.15, 124.47, 124.43, 123.99, 123.73, 123.10, 120.71, 119.17, 119.11, 117.82, 116.42, 54.94, 31.45; elemental analysis: C, 86.14; H, 5.36 %; observed: C, 86.10; H, 5.30%; required HRMS (ESI) m/z of $C_{27}H_{21}O_2^+$ $[M+H]^+$: 377.1542; found: 377.1540.

2.6. Crystallographic Analysis

Crystallographic data have been tabulated as shown in Table 3.

3. RESULTS AND DISCUSSION

3.1. Mechanism of Reaction

During characterization of the products, an interesting observation was that substrates **2h** and **2i** did not yield the expected five-membered *E*-benzofulvene derivatives, instead gave the six-membered products **3h** and **3i,** respectively. The most probable reason may be due to steric factor between remote peri hydrogen and the ketomethyl group (Figure 5) which destabilized the final product.

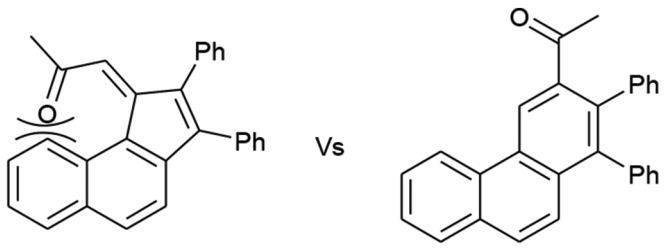


Figure 5: Comparison steric interaction between five and six member ring.

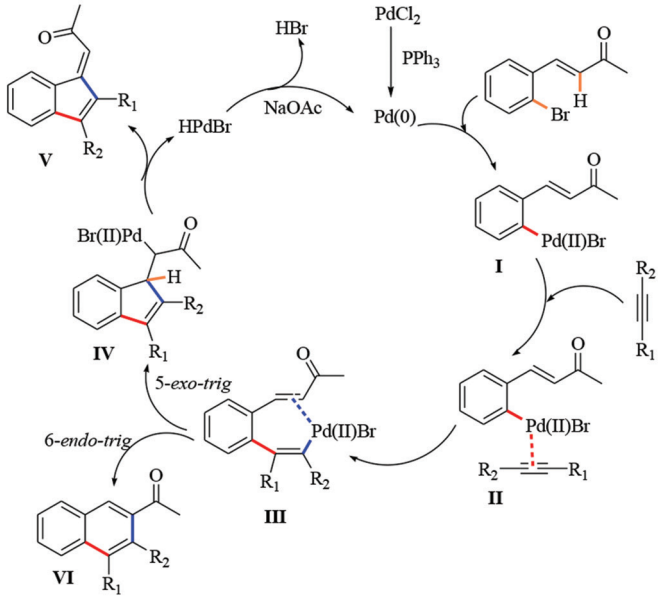


Figure 6: Proposed mechanism.

We proposed that the reaction goes through annulations of internal alkyne with the intermediate **I** to give the carbopalladated intermediate **III** which afforded the intermediate **IV** through *5-exo-trig* cyclization. Final *β*-hydride elimination gave our desired *E*-benzofulvene **V** (Figure 6).

3.2. Density Function Theory (DFT) Study of Reaction mechanism

Furthermore, we support our proposed mechanism by comparing the transition state energies of the probable reaction pathways. The geometry optimization of the two possible (*E*)- and (*Z*)- stereoisomers of 3a and 3g was carried out using the DFT method at the (U)B3LYP level in the Gaussian 09 program [10] and 6-311G* basis set was used for all the elements. The optimized geometries are shown in Figure 7.

The DFT calculation shows that among all the (*E*)- isomers are more stable by 6.78 kcal/mol and 5.25 kcal/mol of energy for **3a** and **3g**, respectively. Fortunately, we have structurally characterized the compound 3**g** by single crystal X-ray diffraction study and it confirmed the (*E*)- isomer. We have compared the calculated and experimental bond lengths and bond angles those are summarized in Table 1 (Supporting information) and it gives reliable values. The electrostatic potential maps on ball-and-spoke model of all the isomers are shown in Figure 8.

It is easily recognized that (*E*)- stereoisomers are more stable than (*Z*)- stereoisomers which is destabilized due to steric hindrance between phenyl ring and keto moiety. In the (*E*)- isomer, the keto moiety is in the opposite side of phenyl rings, whereas all are in same side in case

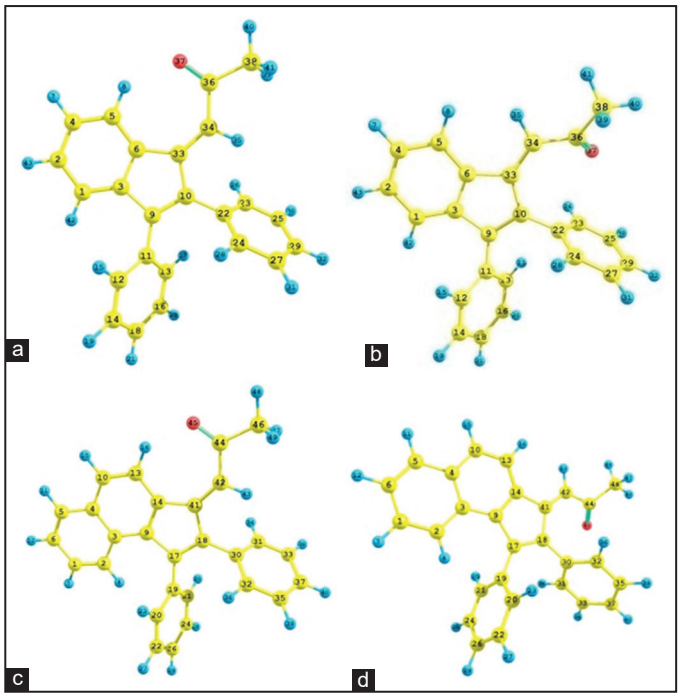


Figure 7: Optimized geometry of (a) (*E*)- isomer and (b) (*Z*)- isomer of **3a** and (c) (*E*)- isomer and (d) (*Z*)- isomer of **3g.**

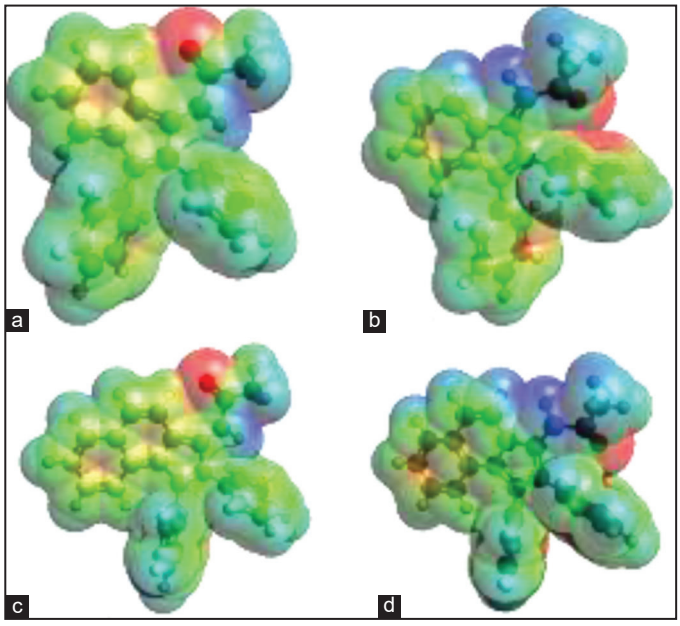


Figure 8: Electrostatic potential maps on ball-and-spoke model of (a) (*E*)- isomer and (b) (*Z*)- isomer of **3a** and (c) (*E*)- isomer and (d) (*Z*)- isomer of **3g** as obtained with DFT/6-311G* calculation.

of (*Z*)- isomers and for that reason, the (*Z*)- isomers are 6.78 kcal/mol and 5.25 kcal/mol for **3a** and **3g,** respectively, more unstable by DFT calculation. All calculation observed NMR spectra and single crystal X-ray diffraction study confirmed that all the isolated products have (*E*)- configuration.

4. CONCLUSION

We have devised a cost-effective and high yielding synthetic route for the synthesis of stereoselective *E*-benzofulvene derivatives using

palladium catalyzed annulations of internal alkyne. Started from easily accessible *o*-bromostyrene and diphenyl acetylene, we obtained benzofulvene exclusively with good to excellent yields. Our developed method has good range of substrate scope and functional group tolerance under very mild reaction conditions. We are hopeful that our method would find further application in organic synthesis.

6. ACKNOWLEDGMENTS

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****Bibliographical Sketch***

Dr. Shubhendu Dhara is an Assistant Professor in the Department of Chemistry, Bhairab Ganguly College, Belgharia, Kolkata-700056. His research interest is Organic Synthesis methodology. He did his Doctoral Degree from Department of Chemistry, IIT, Kharagpur, and Post-Doctoral studies from Schulisch Faculty of Chemistry, Technion-Israel. He has more than 10 years of research experience. He has published 19 national and international peer-reviewed journals. He has been teaching as Assistant Professor in in the Department of Chemistry, Bhairab Ganguly College, Belgharia, Kolkata-700056 since 2017.