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A Rapid and High Efficient Method for Synthesis of Benzofulvenes via CsOH-Catalyzed Condensation of Indene and Aldehydes

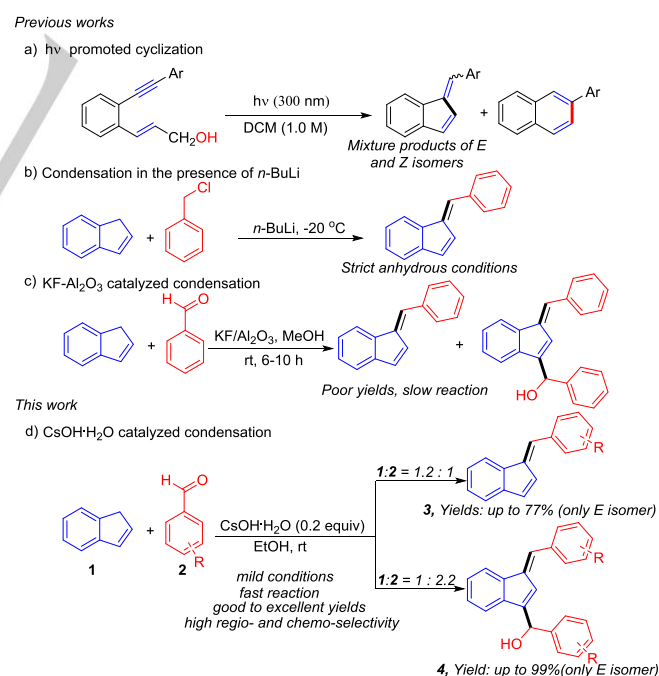
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Abstract: A fast condensation of indene with a wide range of aldehydes catalyzed by cesium hydroxide monohydrate (CsOH·H₂O) for the synthesis of benzofulvenes with good to excellent yields was demonstrated. The condensation can be completed within a few minutes under room temperature and air atmosphere without any use of special ligands or phase-transfer catalysts. In addition, the ratio of indene to aldehydes played an important role in this reaction, the single condensation products **3** can be obtained as main product while 1.2:1, and the double condensation products **4** can be obtained by changing the ratio to 1:2.2. This protocol provides an efficient, simple and general method for the synthesis of benzofulvenes **3** and double condensation products **4**, which are important intermediates in the synthesis of numerous drugs and natural products.

Last decades, more and more attention has been focused on the indene condensation reaction,^[1] because of the wide use of indene derivatives in numerous biologically active compounds.^[2] In addition, indene derivatives such as benzofulvenes are privileged scaffolds in organic chemistry, which have the core structure of many biologically active compounds,^[3] and they have also been used as useful monomers in polymer chemistry,^[4] and they also have found application in material chemistry^[5] and as ligands in metal catalysis.^[6] Due to the important functionality of indene derivatives, efforts are devoted toward their generation.^[7] Although the great success achieved so far in this area, some important challenges still remain: special phase-transfer catalysts (PTC)^[8] must be used in some methods, and others must be performed under harsh reaction conditions^[9] or give poor yields.^[10]

Indene condensation of aldehydes is one of the direct methods for the synthesis of benzofulvenes.^[11] The condensation of benzaldehyde with indene in the presence of calix[4]arene^[8a] or a large amount (10 equiv.) of N-hexadecyltrimethylammonium chloride (CTACl)^[8b] in NaOH aqueous solution were reported. Though good yields were obtained through these methods, expensive phase-transfer

catalyst (PTC) must be used to complete the condensation. The cyclization reaction for the synthesis of benzofulvenes promoted by *hν* was reported by Alabugin and co-workers,^[12] however, the chemo- and regio-selectivity of products are poor for giving the mixture products of *E* and *Z* isomers (Scheme 1, a). Later, Mihan's group reported an efficient route to benzofulvenes via the condensation reaction of indene with benzylchloride in the presence of *n*-butyllithium (Scheme 1, b).^[13] However, the condensation must be performed under strict anhydrous conditions (rigorous drying and -20 °C). The indene condensation reaction catalyzed by a solid catalyst (KF/Al₂O₃) was reported by Yan's group (Scheme 1, c).^[14] However, this condensation gave poor yields both for single and double condensation products. Other process for the preparation of benzofulvenes involves the intramolecular cyclization of *o*-alkynylstyrenes catalyzed by Au,^[15] or in the presence of 3.0 equiv of NIS (*N*-iodosuccinimide)^[16] were reported. Nevertheless, expensive catalysts or toxic reagents must be used in most of these methods, and long reaction time is also needed. Therefore, it is necessary to develop an efficient method that can synthesize benzofulvenes in good yield under mild reaction conditions.



Scheme 1 General methods for the synthesis of benzofulvenes

In addition, cesium hydroxide has been widely used as catalyst in organic chemistry.^[17] In the previous works of our group, cesium hydroxide monohydrate was used as efficient catalyst in the highly regio- and stereo-selective synthesis of (*Z*)-vinylic disulfides^[18] and (*Z*)-vinylic selenosulfides.^[19] During our

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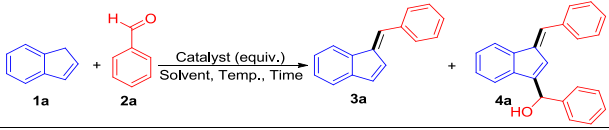
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attempt to develop a rapid way to synthesize benzofulvenes *via* the condensation of indene with aldehydes catalyzed by CsOH·H₂O, we observed that single condensation products **3** and double condensation products **4** can be obtained as main products in *E*-form respectively by easily changing the ratio of indene/aldehydes. Here, we report our work on developing a rapid and highly selective method for the synthesis of benzofulvenes **3** and double condensation products **4** catalyzed by CsOH·H₂O under mild conditions (Scheme 1, d).

We initiated our studies with the condensation reaction of indene **1a** with benzaldehyde **2a** in the presence of 0.2 equiv of CsOH·H₂O at room temperature in DMSO, under air for 2.0 h. Single condensation product **3a** and double condensation product **4a** were obtained in the yield of 42% and 54% respectively, and there was no detection of *Z*-isomer of **4a** or **3a** by ¹H NMR analysis of the crude products.

Table 1. Screening optimal conditions ^a.



Entry	Cat. (equiv.)	Solvent	Temp	Time	n _{1a} /n _{2a}	Yields ^b (%)	
						3a	4a
1	CsOH·H ₂ O (0.2)	DMSO	rt	120 min	1.2:1.0	42	54
2	CsOH·H ₂ O (0.2)	DMSO	rt	10 min	1.2:1.0	50	47
3	CsOH·H ₂ O (0.2)	DMSO	rt	2.0 min	1.2:1.0	52	44
4	CsOH·H ₂ O (0.2)	DMF	rt	2.0 min	1.2:1.0	56	41
5	CsOH·H ₂ O (0.2)	EtOH	rt	2.0 min	1.2:1.0	72(68) ^c	25
6	CsOH·H ₂ O (0.2)	Toluene	rt	2.0 min	1.2:1.0	31	66
7	CsOH·H ₂ O (0.2)	THF	rt	2.0 min	1.2:1.0	55	42
8	CsOH·H ₂ O (0.2)	1,4-dioxane	rt	2.0 min	1.2:1.0	61	36
9	KOH (0.2)	EtOH	rt	2.0 min	1.2:1.0	41	23
10	NaOH (0.2)	EtOH	rt	2.0 min	1.2:1.0	34	20
11	Cs ₂ CO ₃ (0.2)	EtOH	rt	2.0 min	1.2:1.0	30	20
12	K ₂ CO ₃ (0.2)	EtOH	rt	2.0 min	1.2:1.0	24	19
13	Na ₂ CO ₃ (0.2)	EtOH	rt	2.0 min	1.2:1.0	20	16
14	CsOH·H ₂ O (0.5)	EtOH	rt	2.0 min	1.2:1.0	44	52
15	CsOH·H ₂ O (1.0)	EtOH	rt	2.0 min	1.2:1.0	38	57
16	CsOH·H ₂ O (0.2)	EtOH	70 °C	2.0 min	1.2:1.0	52	44
17	CsOH·H ₂ O (0.2)	EtOH	0 °C	2.0 min	1.2:1.0	63	33
18 ^d	CsOH·H ₂ O (0.2)	EtOH	rt	2.0 min	1.2:1.0	72	25
19	CsOH·H ₂ O (0.2)	EtOH	rt	2.0 min	1.8:1.0	65	19
20	CsOH·H ₂ O (0.2)	EtOH	rt	2.0 min	2.0:1.0	60	30
21	CsOH·H ₂ O (0.2)	EtOH	rt	2.0 min	5.0:1.0	39	17
22	CsOH·H ₂ O (0.2)	EtOH	rt	2.0 min	1.0:2.2	5	73
23	CsOH·H ₂ O (0.2)	EtOH	rt	5.0 min	1.0:2.2	5	81
24	CsOH·H ₂ O (0.2)	EtOH	rt	10 min	1.0:2.2	6	94(92) ^c
25	CsOH·H ₂ O (0.2)	EtOH	rt	15 min	1.0:2.2	6	93

Reaction conditions: Indene **1a**, benzaldehyde **2a**, solvent (2.0 mL), air. ^b GC yields. ^c Isolated yields. ^d The reaction was performed under N₂ atmosphere.

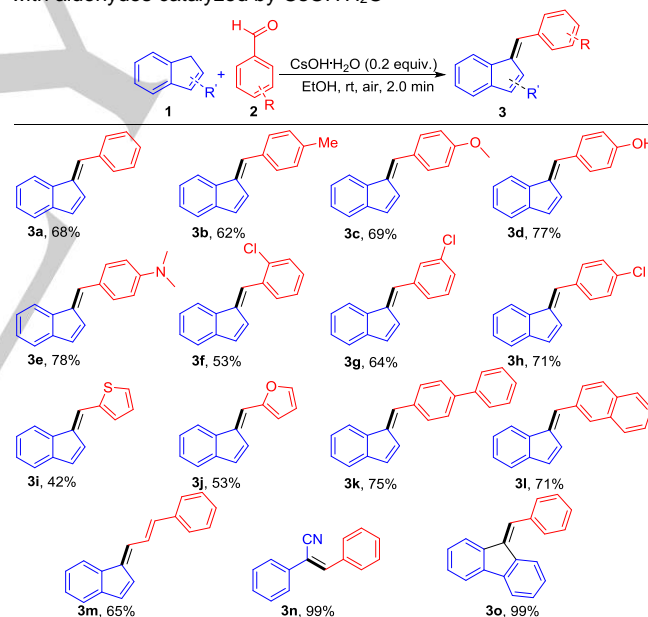
The condensation afforded product **3a** in the yield of 52% by shorting the reaction time to 2.0 min, and the yield of product **4a** was decreased to 44% (Table 1, entries 1-3). After a systematic study on the influence of solvents (such as DMF, EtOH, Toluene, DMSO, THF and 1,4-dioxane) on the reaction (Table 1, entries 3-8), we found that EtOH is the best solvent, and product **3a** was obtained in the yield of 72% (Table 1, entry 5). We also explored the influence of catalysts (such as KOH, NaOH, Cs₂CO₃, K₂CO₃, and Na₂CO₃) to the reaction (Table 1, entries 5, 9-13), and the results shown that the reaction processed slowly when other bases were used as catalysts except for CsOH·H₂O, for giving product **3a** and **4a** both in poor yields. The results also shown that cesium hydroxide was the most suitable catalyst for the product **3a** in 72% yield (Table 1, entry 5). The yield of product **4a** was increased when 1.0 equiv. of CsOH·H₂O was used (Table 1, entries 14-15). The higher temperature (70 °C) was also good for the products **4a** (Table 1, entries 16-17). The influence of nitrogen atmosphere could not

be obtained a higher yield of **3a** (entry 18). We also explored the influence of the ratio of indene **1a** with benzaldehyde **2a** (Table 1, entries 19-22). The yield of single condensation product **3a** was decreased from 65% to 39% when the ratio of **1a** with **2a** was increased from 1.8 to 5.0. However, when the ratio of **1a/2a** was decreased to 0.45, the double condensation product **4a** was obtained as the main product in 94% yield by extending the reaction time to 10 min (Table 1, entry 24). And no higher yield was obtained, when the reaction time was increased to 15 min (Table 1, entry 25).

Thus, the optimized reaction conditions A for **3a** are 0.2 equiv. of CsOH·H₂O, 1.2 equiv. of indene **1a**, 1.0 equiv. of benzaldehyde **2a** in EtOH at room temperature under air for 2.0 min, and the optimized reaction conditions B for **4a** are 0.2 equiv. of CsOH·H₂O, 1.0 equiv. of indene **1a**, 2.2 equiv. of benzaldehyde **2a** in EtOH at room temperature under air for 10 min. And the *E* configuration of **3a** was proven by the NOE experiment (see SI).

To demonstrate the efficiency and generality of the single condensation for synthesis of benzofulvenes **3**, the scope of the reaction was investigated under the optimal conditions A (Table 1, entry 5), and the results are summarized in Table 2.

Table 2. Synthesis of benzofulvenes **3** via condensation of indene with aldehydes catalyzed by CsOH·H₂O ^{a,b}.



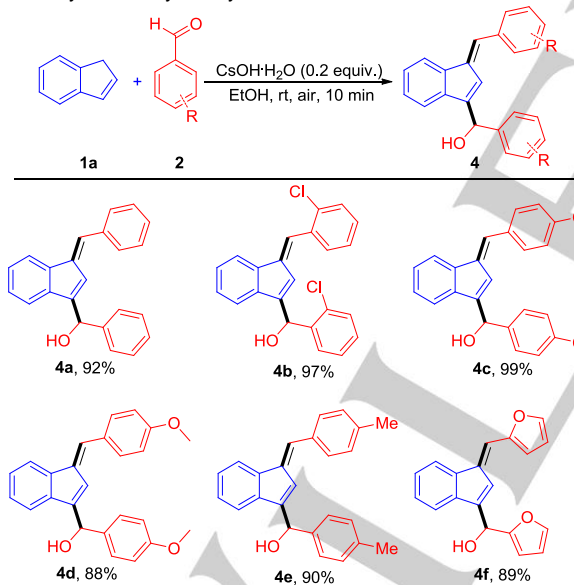
^a Reaction conditions: Indene **1** (1.2 mmol), aromatic aldehydes **2** (1.0 mmol), CsOH·H₂O (0.2 mmol), EtOH (2.0 mL), air, 2.0 min. ^b Isolated yields.

A variety of aldehydes could efficiently undergo condensation to afford the desired products **3** in good to excellent yields. The electron-donating and electron-withdrawing functional groups presenting in the phenyl ring of the aldehydes affected the condensation slightly, for giving the corresponding products in good yields (**3a-3e**, and **3g**). The condensation of indene with *o*-chloro benzaldehyde afforded the desired product **3f** in moderate yield, suggesting that the steric effect of the aromatic aldehyde on the reaction can't be ignored. The condensation is also suitable for 2-thiophenecarboxaldehyde

and furfural, for giving the corresponding products in moderate yields (**3i**, 42% and **3j**, 53%). In addition, the condensation of indene with *p*-phenyl benzaldehyde, 2-naphthalene carboxaldehyde and benzylideneacetaldehyde also give the desired products in good yields (**3k**, 75% and **3l**, 71%, **3m**, 65%). We also extended the procedure to the reaction of benzaldehyde with benzylcyanide or fluorene, and the results shown that desired products **3n** and **3o** were obtained in the yields of 99%. As for isobutyraldehyde, the generation of desired product **3** as detected in TLC analysis was low, mainly due to the lack of conjugacy of the corresponding products which contribute to the stability of (hetero) aromatic products.

However, the reaction of 1.0 equiv of indene with 2.2 equiv. of a variety of aldehydes could efficiently undergo double condensation to afford the corresponding products **4** in excellent yields under the optimal conditions B (Table 1, entry 24). As shown in Table 3, electron-donating (Me, OMe) and electron-withdrawing (Cl) functional groups at the ortho- and para-positions of the phenyl ring of the aldehydes affected the double condensation only slightly, affording the corresponding products in excellent yields (**4b-4f**, 88%-99%). The optimal conditions B was also suitable for double condensation of indene and furfural, for giving the corresponding product **4g** in the yield of 89%. Unfortunately, trace yield was obtained when isobutyraldehyde was treated with indene under the the optimal conditions B.

Table 3. Synthesis of products **3** via double condensation of indene with aldehydes catalyzed by CsOH·H₂O.^{a,b}



^a Reaction conditions: Indene **1a** (1.0 mmol), aromatic aldehydes **2** (2.2 mmol), CsOH·H₂O (0.2 mmol), EtOH (2.0 mL), air, 10 min. ^b Isolated yields.

To shed light on the mechanism of the condensation, the relative energies of the two isomers of *E*-benzofulvene and *Z*-benzofulvene were calculated at the B3LYP/6-31g* level using the Gaussian 09 A.01 package^[20], and the results show that *E*-benzofulvene is more stable than *Z*-benzofulvene, because of the lower relative energies (Figure 1), mainly due to the steric hindrance of the benzene ring.

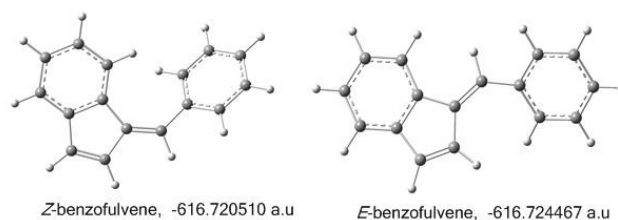
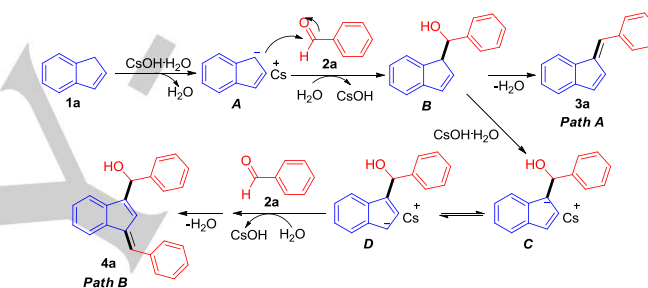


Figure 1. Structures and relative energies of *E*-benzofulvene and *Z*-benzofulvene at B3LYP/6-31g*^a

According to the calculation and previous reports^[8], a plausible mechanism is brought forward (Scheme 2). First, there is the removal of active hydrogen from indene **1a** giving the cesium intermediate **A** as a result. Second, benzaldehyde **2a** reacts with cesium intermediate **A**, then treated with H₂O to give CsOH and specie **B**. The specie **B** can be converted to benzofulvene **3a** by the elimination of H₂O (path A), or reacts with CsOH·H₂O to give specie **C**, which can be converted to specie **D** via the transfer of the electron. The specie **D** reacts with benzaldehyde **2a**, then giving double condensation product **4a** after elimination of H₂O (path B).



Scheme 2. Plausible mechanism of the condensation reaction catalyzed by CsOH·H₂O.

In conclusion, we developed a convenient, simple and rapid procedure for the synthesis of benzofulvenes **3** and double condensation products **4** with good yields and high region- and chemo-selectivity via the condensation reaction of indene with aromatic aldehydes catalyzed by CsOH·H₂O. The method utilizes easily available starting materials, offers operational simplicity, and enjoys a broad substrate scope as well as functionality tolerance. Due to the mild reaction conditions and excellent yields, this work provides a convenient way for the synthesis of benzofulvenes.

Experimental Section

General Procedure for the preparation of compounds 3a-3o: Benzaldehyde **2** (1.0 mmol) was added dropwise to a solution of indene **1** (1.2 mmol) and CsOH·H₂O (0.2 mmol) in 2.0 mL of EtOH. Then the mixture was stirred at 25 °C for 2.0 min. Then the reaction mixture was evaporated in vacuum, and the desired products **3** were obtained by silica gel column chromatograph using ethyl acetate/hexane as an eluent.

General Procedure for the preparation of compounds 4a-4f: Benzaldehyde **2** (2.2 mmol) was added in one portion to a

solution of indene **1** (1.0 mmol) and CsOH·H₂O (0.2 mmol) in 2.0 mL of EtOH. Then the mixture was stirred at 25 °C for 10 min. Then the reaction mixture was evaporated in vacuum, and the desired products **4** was obtained by silica gel column chromatograph using ethyl acetate/hexane as an eluent.

Acknowledgements

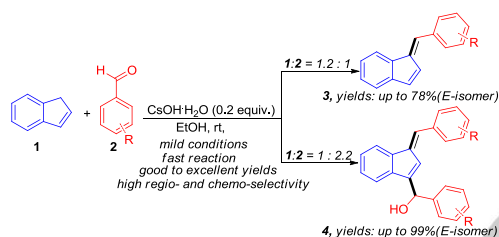
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Keywords: Cesium hydroxide-catalyzed • Condensation Reaction • Benzofulvenes • Aldehydes • Indenes.

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An efficient method for the synthesis of benzofulvenes **3** was demonstrated via the rapid condensation of indene with various of aldehydes catalyzed by cesium hydroxide monohydrate. Single condensation products **3** and double condensation products **4** can be obtained as main products respectively by changing the ratio of the reactants easily.



High regio- and chemo-selectivity, simple and efficient condensation*

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Page No. 1 – Page No. 4
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