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Superacid mediated intramolecular condensation: facile synthesis of indenones and indanones†

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Superacid promoted intramolecular acylation is described for the synthesis of indenones. Interestingly, in all resulting indenones, the olefin bond is rearranged to the *exo* position of the five membered rings. Significantly, the method is further applied to the synthesis of indanones *via* the formation of two C–C bonds by *in situ* treatment of indenones with an external arene, in one-pot. Most importantly, the present sequential method for the synthesis of indanones is advantageous, as it limits even more electron rich external arenes only to the Friedel–Crafts alkylation. This is not possible in previous reports wherein both cinnamic acid ester and the external arenes are treated together in the presence of an acid, wherein the relatively more reactive arene is preferred to facilitate the acylation step.

Among the classical reactions for the creation of C–C bonds, the Friedel–Crafts reaction turned out to be one of the most powerful techniques towards aromatic electrophilic substitutions.¹ In particular, for the past few decades there were numerous applications of this reaction under different acidic conditions (Brønsted/Lewis).^{2–4} Particularly, the intramolecular acylation of this protocol was found to be ideal as it constructs the carbocyclic systems; many natural products and drugs are cyclic compounds. In this regard, indanones and indenones are essential carbocyclic compounds as they constitute natural as well as pharmaceutical products. Some of the biologically important natural and unnatural indanones/indenones are shown in Fig. 1.⁵ Their interesting biological activities prompted organic chemists to develop new synthetic methods towards their synthesis. In the past decades, many methods have been developed for the synthesis of indanones/indenones. For example, indanones were synthesized using the Friedel–Crafts, Rh-catalysis⁶ and Nazarov cyclizations.⁷ Also, indenones were

prepared by employing the Friedel–Crafts and metal-catalysed reactions.⁸ Some notable Pd-catalyzed annulations for the synthesis of indenones have been noted from the research groups of Larock,⁹ Chiusoli,¹⁰ Buchwald¹¹ and Li.¹² Nagao¹³ *et al.* reported the formation of indenones from allenyl aryl ketones upon treatment with $\text{BF}_3 \cdot \text{OEt}_2$. Liang and co-workers disclosed the synthesis of indenones under gold catalyzed tandem rearrangement.¹⁴ While, the research group of Ohwada reported triflic acid promoted cyclization for the synthesis of indenones and dihydro naphthalenes.¹⁵ Womack disclosed synthesis of indanones and indenols from 2-alkylcinnamaldehydes *via* intramolecular Friedel–Crafts reaction using FeCl_3 .¹⁶ On the other hand, Klumpp¹⁷ and Fillion¹⁸ co-workers reported the synthesis of indanones under Friedel–Crafts acylation conditions.

Normally, the classical intramolecular Friedel–Crafts acylation works between an acyl halide or carboxylic acid or anhydride with an aromatic ring under acid promoter (Lewis or Brønsted). Lewis acid promoted intramolecular Friedel–Crafts acylation of acyl halides are not familiar. Whereas, intramolecular acylation protocols by direct use of carboxylic acids

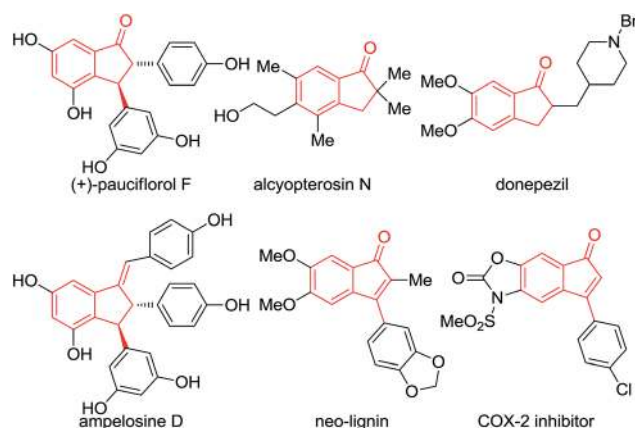


Fig. 1 Naturally occurring and pharmaceutically important indanones/indenones.

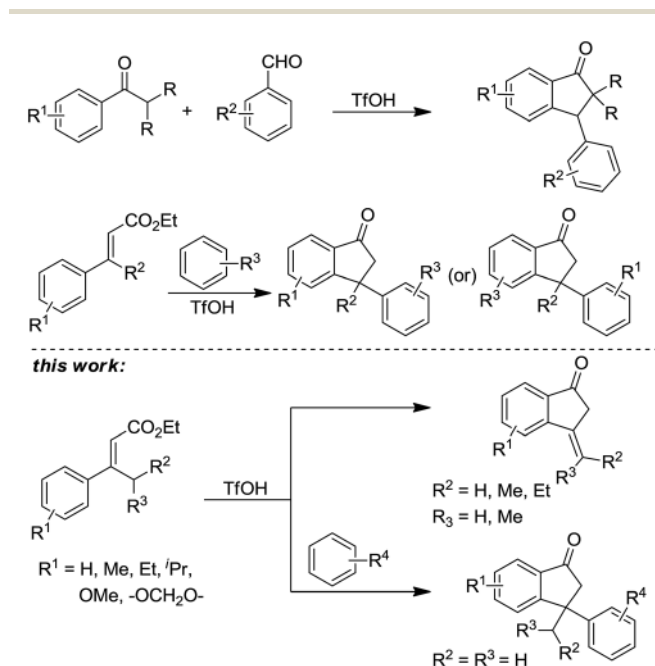
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as carbocation equivalents suffer due to the poor leaving nature of the hydroxyl group, hence require forceful conditions. For Meldrum's acids, competition studies for the rate of intramolecular acylation is determined to be tetralone > benzosuberone > indanone. Therefore, synthesis of five-membered ketones (1-indanones) might be feasible under harsh conditions. In addition, direct synthesis of indanones starting from esters using intramolecular Friedel–Crafts acylations are not familiar. However, use of Meldrum's acid for the synthesis of carbocyclic ketones under mild Friedel–Crafts conditions is very good alternative. In 2008, the research group of Baba reported¹⁹ acylation of arenes with esters by dimethylchlorosilane and indium tribromide. As part of our ongoing research interests in domino or sequential domino one-pot process, very recently, we have developed a super acid promoted synthesis of indanones starting from simple cinnamic acid esters.²⁰ In this study, the generality and scope of this method has been well studied by synthesizing numerous compounds. We also developed a practical method for the direct synthesis of highly substituted indanones from very simple aryl isopropyl ketones and benzaldehydes promoted by super acid (Scheme 1).²¹ Though, the Friedel–Crafts cycloacylation was known with acid chlorides and carboxylic acids, the corresponding esters have not been used for this purpose. This may be due to their less reactivity. With this back ground, we envisioned that the direct treatment of simple cinnamic acid esters under strong acidic conditions, would lead to the formation of indenones. Here in, we describe an efficient and practical method for the synthesis of indenones using triflic acid as the promoter under Friedel–Crafts acylation conditions. To the best of our knowledge, there were no reports on the direct intramolecular acylation of cinnamic acid esters. Also, unlike our previous report(s), the present method was applied for the synthesis of indanones in a sequential one-pot

manner. In the earlier report for synthesis of indanones, relatively more electron rich aromatic ring was involved in acylation step. Whereas, the present sequential strategy, allows the acylation exclusively by the ring that is derived from cinnamic acid ester, thereby limiting the external arene only to alkylation step irrespective of its reactive nature.

To initiate the synthetic study, the required β -alkyl cinnamates **1** were readily synthesized from the corresponding carbonyl compounds (benzaldehydes or corresponding ketones) under standard Wittig–Horner–Wadsworth–Emmons conditions. As a model study, the β -methyl cinnamic acid ester **1a** was explored under different set of acidic conditions to sort out optimized conditions and the results are as summarized in Table 1. Therefore, initially our previously established conditions for the synthesis of indanones were applied on β -methyl cinnamic acid ester **1a**. However, no progress was seen and led to recovery of the starting material **1a** (Table 1, entry 1). Almost same trend has been noticed with CHCl_3 and Lewis acids (FeCl_3 and $\text{BF}_3 \cdot \text{OEt}_2$) as well (Table 1, entries 2–4). Neither the product **2a** nor the starting material **1a** was isolated when H_2SO_4 and AlCl_3 were used (Table 1, entries 5–6). Interestingly, the expected product **2a** was observed but with the double bond isomerization to *exo*-cyclic position of the five membered ketone by increasing the amount of TfOH (Table 1, entry 7). Interestingly, further increase of TfOH (20 equiv.), gave the indenone **2a** in fair yield (Table 1, entry 8). Gratifyingly, the reaction with 24 equiv. of TfOH, furnished the indenone **2a** in very good yield (87%, Table 1, entry 9). However, no progress was noticed with more equivalents of mild Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$ (Table 1, entry 10). Significantly, the preference of rearranged olefin bond to



Scheme 1 Comparison of the present vs. previous approaches.

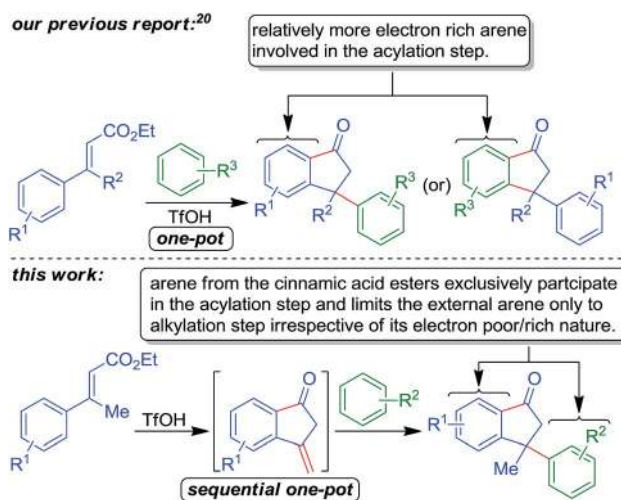
Table 1 Optimizing conditions for the formation of indenone **2a** starting from **1a**

Entry ^a	Acid (equiv.)	Solvent (mL)	Temp (°C)	Time (h)	Yield ^b (%)
1	TfOH (3)	DCE (2)	80	12	0 ^c
2	TfOH (3)	CHCl_3 (2)	80	12	0 ^c
3	FeCl_3 (3)	DCE (2)	80	12	0 ^c
4	$\text{BF}_3 \cdot \text{OEt}_2$ (3)	DCE (2)	80	12	0 ^c
5	H_2SO_4 (3)	DCE (2)	80	12	— ^d
6	AlCl_3 (3)	DCE (2)	80	12	— ^d
7	TfOH (10)	DCE (2)	RT	12	50% ^e
8	TfOH (20)	DCE (2)	RT	12	72%
9	TfOH (24)	DCE (2)	RT	8	87%
10	$\text{BF}_3 \cdot \text{OEt}_2$ (20)	DCE (2)	80	12	0 ^c

^a All reactions were carried out on 95 mg (0.5 mmol) scale of **1a** and solvent DCE (2 mL). ^b Yields of chromatographically pure products. ^c Only starting material **1a** was recovered. ^d Neither the product **2a** nor starting material **1a** was recovered. ^e Starting material **1a** was also recovered.

the *exo* position to ring reveals its unusual stability over the *endo* double bond isomer. This present study is further supported by the previous reports for the synthesis of indenones under various conditions, wherein the olefin bond is placed at *exo* position of the ring as well.^{10–14}

To check the scope and generality of the method, we have applied the above established conditions (Table 1, entry 9) to other β -alkyl cinnamic acid esters **1b–1t** and the results are as summarized in Table 2. Delightfully, the protocol was quite successful and amenable for the systems with different substituents and gave the corresponding indenones **2a–2t** with di-, tri- and tetra-substituted *exo*-cyclic olefins, in very good to excellent yields (Table 2). It is worth mentioning that in the case of similar aromatic systems such as phenyl/naphthyl/alkyl substituent on the ring (**2a**, **2f**, **2g**, **2o**, **2p** & **2q**), the reaction was quite successful under established conditions [*i.e.* TfOH (24 equiv.), 8 to 12 h, RT]. On the other hand, usually, the reaction with electron rich aromatic rings (**2b–2e**, **2h–2n** & **2r–2t**) completed quickly even with low amount of triflic acid (3 equiv.). Notably, the substrate scope has been well studied

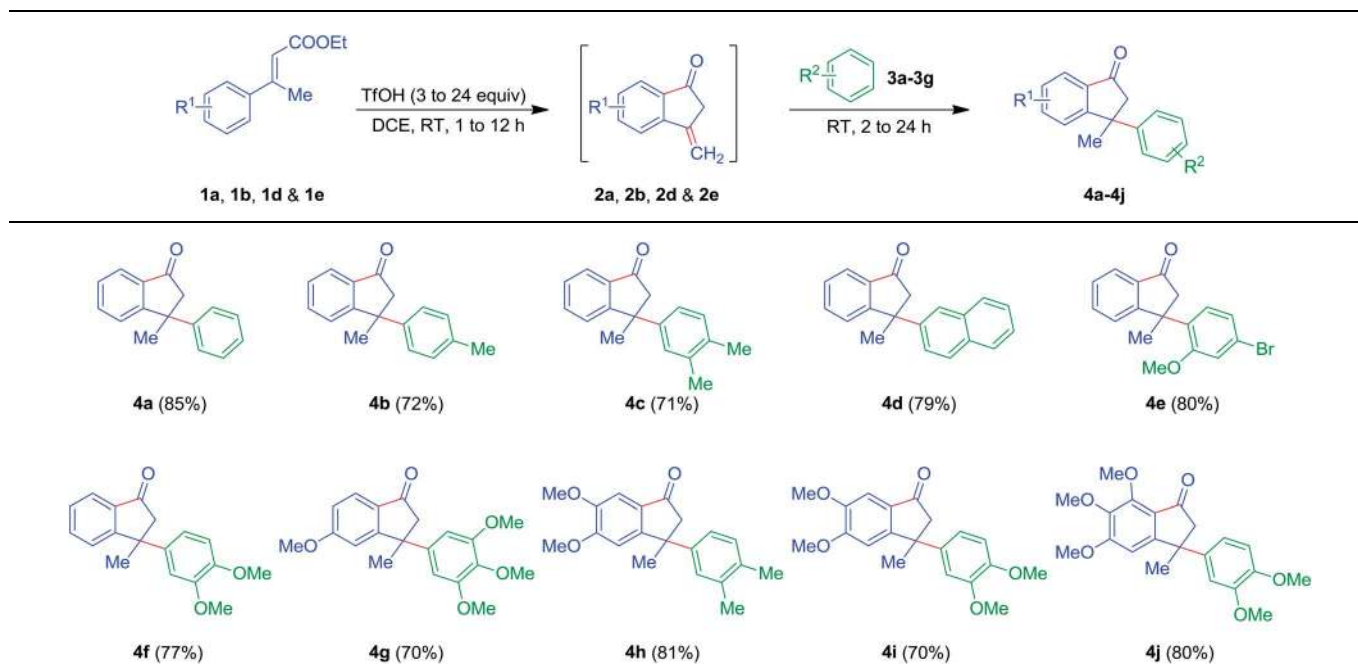


Scheme 2 Comparing the technical differences between the present and previous results.

Table 2 Synthesis of indenones **2** via intramolecular acylation from cinnamic acid esters **1**^{a,b}

<p>TfOH (24 equiv) RT, 8 h (2a, 87%)</p>	<p>TfOH (24 equiv) RT, 6 h (2b, 77%)</p>	<p>TfOH (24 equiv) 0 °C, 30 min (2c, 76%)</p>	<p>TfOH (24 equiv) RT, 1 h (2d, 75%)</p>	<p>TfOH (24 equiv) RT, 1 h (2e, 72%)</p>
<p>TfOH (24 equiv) RT, 8 h (2f, 66%)</p>	<p>TfOH (24 equiv) RT, 12 h (2g, 79%)</p>	<p>TfOH (3 equiv) RT, 5 h (2h, 80%)</p>	<p>TfOH (3 equiv) 0 °C to RT, 2 h (2i, 56%)</p>	<p>TfOH (3 equiv) RT, 1 h (2j, 98%)</p>
<p>TfOH (3 equiv) RT, 1 h (2k, 95%)</p>	<p>TfOH (3 equiv) RT, 4 h (2l, 86%)</p>	<p>TfOH (3 equiv) RT, 4 h (2m, 98%)</p>	<p>TfOH (3 equiv) RT, 4 h (2n, 99%)</p>	<p>TfOH (24 equiv) RT, 12 h (2o, 81%)</p>
<p>TfOH (24 equiv) RT, 12 h (2p, 60%)</p>	<p>TfOH (24 equiv) RT, 12 h (2q, 68%)</p>	<p>TfOH (3 equiv) 0 °C to RT, 1 h (2r, 78%)</p>	<p>TfOH (3 equiv) RT, 1 h (2s, 91%)</p>	<p>TfOH (3 equiv) RT, 1 h (2t, 98%)</p>

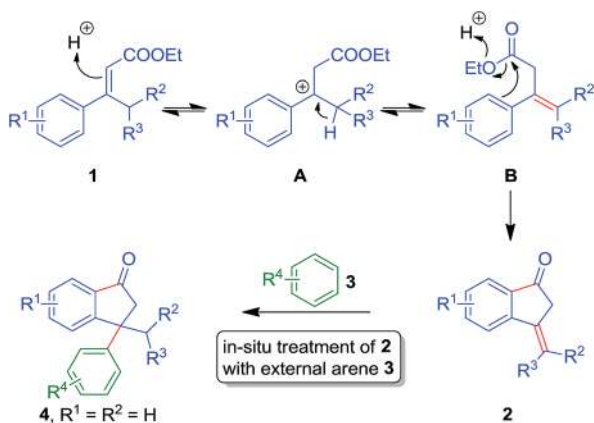
^a All reactions were carried out on 0.5 mmol scale of **1**. ^b Yields of chromatographically pure products.

Table 3 Synthesis of indanones **4** from cinnamic acid esters **1** via intramolecular acylation and intermolecular arylation^{a,b}

^a All reactions were carried out on 0.5 mmol scale of **1**. ^b Yields of chromatographically pure products.

with simple to electron rich aromatic rings and with different β -alkyl substituents (methyl, ethyl, *n*-propyl & iso-propyl) as well. Unless otherwise noted, for each system, the reaction was explored at least two to four times, under varying amount of the acid and time, and the best conditions are presented in Table 2. In addition to the NMR data for the stereochemistry of the *exo*-cyclic olefin is unambiguously confirmed from the single crystal X-ray diffraction analysis of **2m** (see, ESI†).

Furthermore, to extend the method, synthesis of substituted indanones containing quaternary carbon atom was planned, in a sequential one-pot manner. It was anticipated that treatment of *in situ* generated indenone with an external arene would deliver indanones in a complimentary mode to our previous method for the synthesis of indanones (Scheme 2).²⁰



Scheme 3 Plausible reaction mechanism for the formation of indenones **2** and indanones **4**.

Gratifyingly, as expected, the sequential one-pot protocol was found successful and furnished the corresponding indanones **4a–4j** (Table 3). Significantly, unlike our previous method for the synthesis of indanones (in which the relatively more electron rich aromatic ring selectively participated in the Friedel-Crafts acylation step), the present method limits the external arene to only Friedel-Crafts alkylation irrespective of its electron poor/rich nature. However, the reaction was smooth for simple acetophenone derived cinnamic acid esters, but in case of higher β -alkyl cinnamic acid esters, the reaction was not successful. This may be due to more thermodynamic stability of more substituted double bond of the intermediate indenone **2**. On the other hand, under forceful conditions led to the decomposition of the reaction mixture.

A plausible reaction mechanism for the formation of indenones **2** and indanones **4** is shown in Scheme 3. Initially, the protic acid could activate and isomerize the double bond of the ester **1** to yield the equilibrating structures **A** and **B**. Intramolecular acylation of **B** and rearomatization leads to the indenone **2**. Further, *in situ* treatment of indenone **2** with an external arene **3** affords indanone **4**.

Conclusions

We have disclosed an efficient method for the synthesis of indenones *via* intramolecular Friedel-Crafts acylation and double bond isomerization of cinnamic acid esters. Further, the protocol was extended to the synthesis of indanones by treatment of *in situ* generated indenones with external arenes. Notably, the present method limits the external arene only to

the Friedel–Crafts alkylation which was not possible in our previous protocol for the synthesis of indanones.

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