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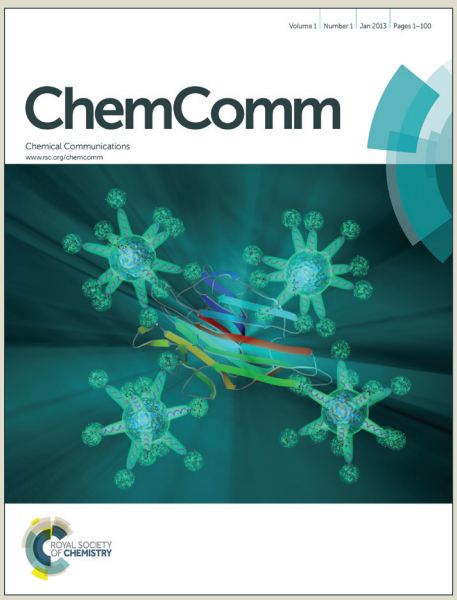

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$FeCl_3$ Mediated Synthesis of Substituted Indenones by Formal [2+2] Cycloaddition/Ring Opening Cascade of *O*-Keto-Cinnamates

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A novel $FeCl_3$ mediated formal [2+2] cycloaddition/ring opening cascade of *o*-keto-cinnamates was developed for the synthesis of indenones. The reaction tolerates a broad range of functional groups, including bromide, chloride, amide, acid and ester groups.

The use of environmentally benign, mild iron catalysis in organic synthesis is still emerging.[1] The iron catalysed/mediated reactions has generated considerable interest in organic synthesis because of their unique reactivity, the diversity of transformations that can be achieved and the extremely high functional group tolerance.[1] Our interest in the iron catalysed/mediated reactions for the C-C bond formation culminated into the discovery of new reactions.[2] We report here an interesting finding of $FeCl_3$ mediated formation of highly substituted indenone derivatives by formal [2+2] cycloaddition /ring opening cascade of *o*-keto cinnamates. Indane motif is found in many biologically active compounds such as (+)-indatraline (**1**), a nonselective monoamine transporter inhibitor to block the reuptake of dopamine, norepinephrine and serotonin [3](fig. 1). It is also found in naturally occurring molecules from resvetrol family quadranglularin A (**2**),[4a,b] parthenocissin A (**3**)[4c,d]

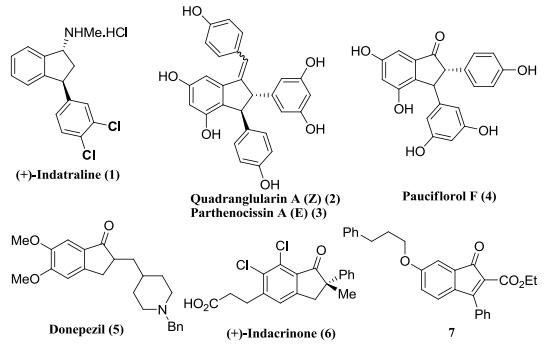
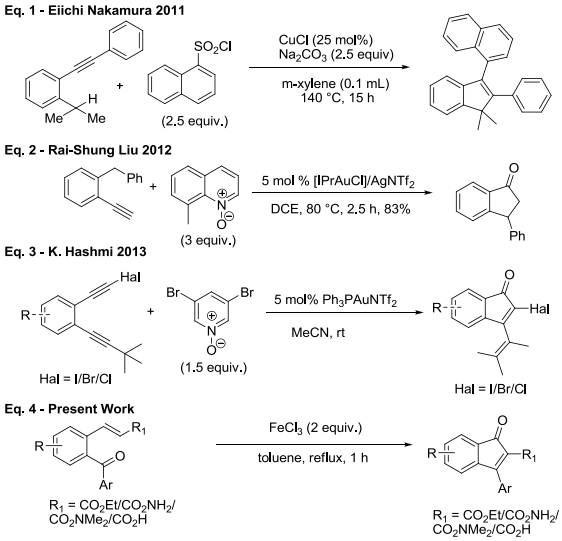


Fig 1: Representive example of natural and unnatural indanones/indenes and its derivatives.



Scheme 1: Method for synthesis of indanone derivative.

and pauciferol F (**4**).[4e] Additionally, indenone derivatives donepezil (**5**)[5a] and indacrinone (**6**)[5b,c] have been developed as Alzheimer and antihypertensive drugs respectively. Indenone (**7**) shows agonist activity against PPAR (γ), which is useful for the treatment of type diabetes (Fig. 1).[6] Indenone based compounds are also used intermediate in pharmaceuticals,[7a-c] conducting polymers,[7d] ligand for metallocene complexes[7e,f] and in material science as discot liquid crystals.[7g] Due to their synthetic utility and application pharmaceuticals, variety of synthetic methods have been developed for the synthesis of indenones. Among thes intramolecular Friedel-Crafts[8] and Nazarov cyclization[9] reactions are the most common methods found in literature. In addition to is, number of metal catalysts has been used for the synthesis indenones (some of them are summarised in Scheme 1). Recentl Nakamura *et. al.* reported an elegant, copper-catalyzed arylativ cyclization of arylalkynes with aromatic sulfonyl chlorides for th synthesis of polysubstituted 1H-indenes (Scheme 1, eq.-1).[10] Synthesis of indenone and its derivatives was achieved by Liu *et. a* using gold-catalyzed cyclization reaction of *cis*-3-en-1-ynes (Scheme 1, eq.-2).[11] In 2013 Hashmi *et. al.* developed an excellent gol catalyzed oxidative diyne cyclizations via 1,6-carbene transfer for

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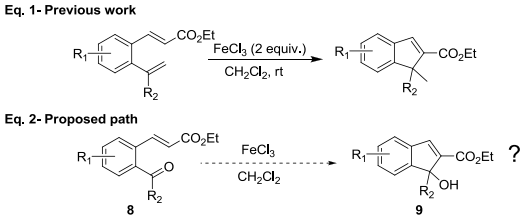
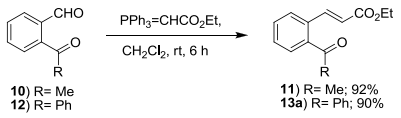
† This work is dedicated to Dr. J. S. Yadav on the occasion of his 65th birthday.

the synthesis of indenones (Scheme 1, eq.-3).[12] Although all these methods are catalytic they require super stoichiometric amount of



Scheme 2. Work plan.



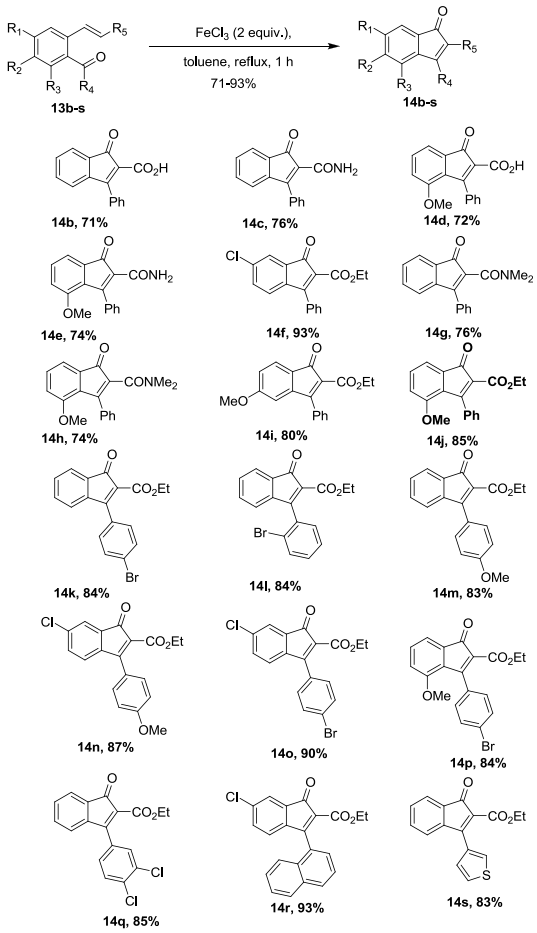
Scheme 3: Synthesis of keto-cinnamate.

Table 1. Optimization of cyclisation reaction.

Entry	Catalyst (2 equvi.)	Solvent	Temp.	Time	Yield
1	$FeCl_3$	CH_2Cl_2	r.t.	12 h	C.R.M.
2	$FeCl_3$	CH_3CN	r.t.	12 h	N.R.
3	$FeCl_3$	CH_3CN	reflux	12 h	45%
4	$FeCl_3$	THF	reflux	12 h	N.R.
5	$FeCl_3$	Toluene	reflux	1 h	87%
6	$FeCl_3.6H_2O$	CH_3CN	reflux	12 h	N.R.
7	$Fe(OTf)_3$	CH_3CN	reflux	24 h	N.R.
8	$TiCl_4$	Toluene	reflux	1 h	N.R.
9	$AlCl_3$	Toluene	reflux	1 h	C.R.M.
10	$BF_3.OEt_2$	CH_3CN	r.t.	24 h	N.R.
11	$BF_3.OEt_2$	CH_2Cl_2	r.t.	12 h	C.R.M.
12	$BF_3.OEt_2$	Toluene	reflux	12 h	C.R.M.

external additive/oxidant (Scheme 1, eq.-1, 2, 3). Herein we report the novel approach of $FeCl_3$ mediated cascade for synthesis of highly substituted indenones (Scheme 1, eq.-4). Recently we have developed an olefin-cation cyclization reaction of cinnamates (Scheme 2, eq.-1).[2a] On similar lines we became interested in reaction of ortho keto-cinnamates **8** using $FeCl_3$ to generate the indenol derivative **9** (Scheme 2, eq.-2). Although such kind of intramolecular attack on ketone is unprecedented in literature, we thought of tuning the reaction conditions and substrate to take the reaction in forward direction for the synthesis of indenol **9** (Scheme 2, eq.-2).

To begin with required keto-cinamate **11** was prepared by regioselective Wittig reaction on aldehyde **10**, using $PPh_3=CHCO_2Et$ in CH_2Cl_2 (scheme 3). Once keto-cinnamate **11** in hand, it was treated with $FeCl_3$ (2 equiv.) in CH_2Cl_2 at room temperature, but to our disappointment we didn't observe any reaction and recovered the starting material. No change in starting material was observed in presence of $FeCl_3$ after changing solvent from CH_2Cl_2 to THF, toluene or acetonitrile at room temperature as well as under reflux condition. At this stage, it was contemplated that $FeCl_3$ mediated intramolecular nucleophilic attack could be facilitated by increasing the electrophilic character of keto group, which could be achieved by changing the R group in compound **11** from alkyl to aromatic fo



Scheme 4. Various indenone derivatives.

further polarization of keto group. To quickly check our assumption *o*-keto-cinnamate **13a** was synthesized from aldehyde **12** in one step by regioselective Horner-Wadsworth-Wittig reaction. Although we observed complex reaction mixture after reaction of compound **13a** with $FeCl_3$ (2 equiv.) in CH_2Cl_2 at room temperature, to our delight compound **13a** on treatment with $FeCl_3$ (2 equiv.) in acetonitrile under reflux conditions was converted directly into indenone **14a** in 45% yield instead of expected indenol **9**. To improve the yield of this transformation, we examined various catalysts as well as solvents which is summarised in table 1. Among the catalyst screened, use of 2 equivalent $FeCl_3$ and $BF_3.OEt_2$ in acetonitrile at room temperature failed to generate **14a** from **13a** (entry 2 and 10, Table 1) and $BF_3.OEt_2$ in CH_2Cl_2 at room temperature formed complex reaction mixture (entry 12, Table 1). $FeCl_3$ in THF and $TiCl_4$ in toluene reflux condition failed to generate any product **14a** and starting material **13a** was recovered (entry 4 and 8, Table 1). Complex reaction mixture was observed in case

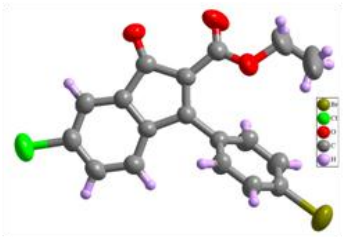
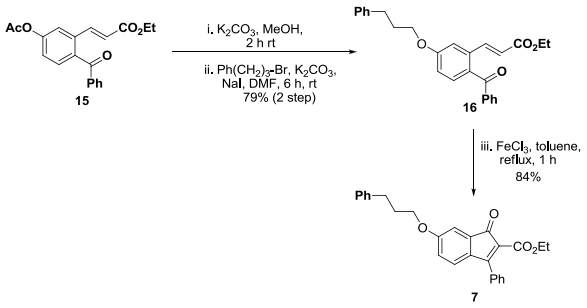


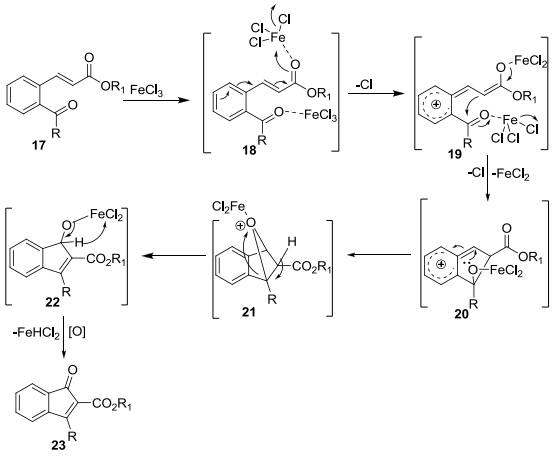
Fig 2: Ortep diagram of indenone **14o**.[13]

$AlCl_3$ and $BF_3.OEt_2$ under toluene reflux condition (entry 9 and 12, Table 1). Cinnamate **14a** was remained unreacted when treated with $FeCl_3.6H_2O$ and $Fe(OTf)_3$ under acetonitrile reflux condition (entry 6 and 7, Table 1). In the presence of other metal catalyst ($CuCl_2$, CuCl, CuI, $NiCl_2$, $PtCl_2$ and $PdCl_2$) this reaction did not proceed at all. Interestingly, after screening various solvent and catalyst combination, it was found that the use of $FeCl_3$ (2 equiv.) and toluene as solvent under reflux condition for 1 h, leads to the formation of **14a** in 87% yield (entry 5, Table 1). Use of catalytic amount of $FeCl_3$ (10 mol%) afforded indenone **14a** from **13a** in less than 10% yield, showing the need of stoichiometric amount of $FeCl_3$ to effect this transformation.



Scheme 5. Synthesis of indenone **7**.

To check the substrate scope of this reaction, we prepared various keto-cinnamates **13b-q** by varying substitution on both the aromatic rings (see supporting information for the preparation). Keto-cinnamates **13b**-**q** converted into respective indenone derivatives **14b**-**q** in good yields. As illustrated in scheme-4 it was observed that, this reaction can tolerate different functional groups such as bromide (**14k**, **14l** and **14m**), chloride (**14f**, **14o**, **14q, 14r** and **14n**), methoxy (**14i** and **14j**), carboxylic acid (**14b** and **14d**), amide (**14c**, **14h**, **14e** and **14g**) and ester (**14a**, **14p** and **14s**). Keto-cinnamate **13r** and **13s**, containing naphthalene and thiophene ring on carbonyl carbon also converted smoothly into indenone **14r** and **14s** in 93% and 83% yield respectively, further expanding the scope of the reaction. The structure of indenone derivative was further established by single crystal X-ray analysis of compound **14o** (Fig. 2).[13] This method was also applied for the synthesis indenone **7**, which shows agonistic activity with an EC_{50} value of 50 nM, and could be useful for the treatment of type 2 diabetes.[6] To begin with compound **15** (see supporting for preparation) was subjected for the hydrolysis of acetate using K_2CO_3 in MeOH at room temperature followed by protection of resultant hydroxy group with 3-bromopropyl benzene to furnish the required keto-cinamate **16** in 79% yield. Then using $FeCl_3$ mediated cascade



Scheme 6. Plausible mechanism.

cyclization reaction, keto-cinnamate **16** was converted indenone **7** in 84% yield (Scheme 5). We were surprised by the indenone product **14** formation as it requires transfer of oxy atom of keto group of compound **13** to form the keto group indenone **14**. At this stage although we do not have any proof for mechanism of this reaction, a plausible mechanism is proposed f this transformation as shown in scheme 6. Reaction of keto-cinnamate **17** with $FeCl_3$ could generate conjugated enolate **1** which on further rearrangement forms oxa-bridged intermediate **2** via **20** by attack of enolate on Lewis acid activated ketone at orth position of aromatic ring, followed by rearomatization. Loss acidic proton followed by subsequent opening of bridged syste generates indenole **22**, which on iron mediated oxidation affor indenone **23**.

In conclusion, we have developed a novel cascade approach for th synthesis of highly substituted indenones using environmentall benign and abundantly available catalyst $FeCl_3$. It was observed to carry out this transformation biaryl system attached to carbonyl carbon is necessary to increase the electrophilicity of the carbonyl group. High functional group tolerance of this reaction allow access to various indenones for further application pharmaceutical and material chemistry.

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Notes and references

1 (a) E. Nakamura, T. Hatakeyama, S. Ito, K. Ishizuka, L. Ilies and M. Nakamura, *Organic Reactions, Ed.; S. E. Denmark, John Wiley and Sons, Inc.*, 2014, 83*;* For reviews on the iron Lewis acid catalysis, see: (b) C. Bolm, J. Legros, J. L. Paih and L. Zani, *Chem. Rev.,* 2004, **104**, 6217; (c) E. Nakamura and N. Yoshikai, *J. Org. Chem.*, 2010, **75**, 6061; (d) J. I. Padron, and V. S. Martin, *Top. Organomet. Chem.,* **2011**, *33*, 1.

2 (a) D. H. Dethe, and G. M. Murhade, *Chem. Commun.*, 2013, **49**, 8051; (b) D. H. Dethe and G. Murhade, *Org. Lett.*, 2013, **15**, 429; (c) D. H. Dethe, R. Boda and G. M. Murhade, *Org. Chem. Front.*, 10.1039/c5qo00005j.
3 K. Hyttel and J. -J. Larsen, *J. Neurochem.*, 1985, **44**, 1615.
4 (a) S. A. Adesanya, R. Nia, M.-T. Martin, N. Boukamcha, A. Montagnac and M. Pais, *J. Nat. Prod.*, 1999, **62**, 169; (b) W. Li, H. Li, Y. Li and Z. Hou, *Angew. Chem. Int. Ed.*, 2006, **45**, 7609; (c) T. Tanaka, M. Iinuma and H. Murata, *Phytochemistry*, 1998, **48**, 1045; (d) H. J. Kim, M. Saleem, S. H. Seo, C. Jin and Y. S. Lee, *Planta Med.*, 2005, **71**, 973; (e) T. Ito, T. Tanaka, M. Iinuma, K. I. Nakaya, Y. Takahashi, R. Sawa, J. Murata and D. Darnaedi, *J. Nat. Prod.*, 2004, **67**, 932.
5 (a) H. Sugimoto, Y. Iimura, Y. Yamanishi and K. Yamatsu, *J. Med. Chem.*, 1995, **38**, 4821; (b) U. -H. Dolling, P. Davis and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1984, **106**, 446; (c) S. J. De Solms, O. W. Jr. Woltersdorf and E. J. Jr. Cragoe, *J. Med. Chem.*, 1978, **21**, 437.
6 J. H. Ahn, M. S. Shin, S. H. Jung, S. K. Kang, K. R. Kim, S. D. Rhee, W. H. Jung, S. D. Yang, S. J. Kim, J. R. Woo, J. H. Lee, H. G. Cheon and S. S. Kim, *J. Med. Chem.*, 2006, **49**, 4781.
7 (a) H. Sugimoto, *Pure Appl. Chem.*, 1999, **71**, 2031; (b) H. Schumann, O. Stenzel and F. Girgsdies, *Organometallics*, 2001, **20**, 1743; (c) M. N. Herzog, J. C. W. Chien and M. D. Rausch, *J. Organomet. Chem.*, 2002, **654**, 29; (d) J. Yang, M. V. Lakshmikantham and M. P. Cava, *J. Org. Chem.*, 2000, **65**, 6739; (e) R. Leino, P. Lehmus and A. Lehtonen, *Eur. J. Inorg. Chem.*, 2004, 3201; (f) D. Leinweber, I. Weidner, R. Wilhelm, R. Wartchow and H. Butenschçn, *Eur. J. Org. Chem.*, 2005, 5224; (g) M. J. Barber, O. A. Rakitin, M. B. Ros and T. Torroba, *Angew. Chem. Int. Ed.*, 1998, **110**, 308.
8 (a) D. -M. Cui, C. Zhang, M. Kawamura and S. Shimada, *Tetrahedron Lett.*, 2004, **45**, 1741; (b) E. Fillion, D. Fishlock, A. Wilsily and J. M. Goll, *J. Org. Chem.*, 2005, **70**, 1316.
9 (a) N. J. Lawrence, E. M. S. Armitage, B. Greedy, D. Cook, S. Ducki and A. T. McGown, *Tetrahedron Lett.*, 2006, **47**, 1637; (b) W. Yin, Y. Ma, J. Xu and Y. Zhao, *J. Org. Chem.*, 2006, **71**, 4312.
10 (a) X. Zeng, L. Ilies and E. Nakamura *J. Am. Chem. Soc.*, 2011, **133**, 17638; (b) X. Zhu, C. Mitsui, H. Tsuji and E. Nakamura, *J. Am. Chem. Soc.*, 2009, **131**, 13596.
11 S. Bhunia, S. Ghorpade, D. B. Huple and R. –S. Liu, *Angew. Chem. Int. Ed.*, 2012, **51**, 2939.
12 P. Nosel, L. N. S. Comprido, T. Lauterbach, M. Rudolph, F. Rominger and A. S. K. Hashmi, *J. Am. Chem. Soc.*, 2013, **135**, 15662.
13 CCDC 1035484 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.