Tetrahedron Letters 50 (2009) 4978–4982

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient synthesis of indenes by $FeCl_3·6H_2O$-catalyzed intramolecular Friedel–Crafts reaction of aryl-substituted allylic alcohols

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ARTICLE INFO

Article history:
Received 15 April 2009
Revised 6 June 2009
Accepted 12 June 2009
Available online 16 June 2009

ABSTRACT

An efficient procedure for the synthesis of substituted indenes through the $FeCl_3·6H_2O$-catalyzed intramolecular Friedel–Crafts cyclization of aryl-substituted allylic alcohols has been developed. This method features the easily available starting materials, cheap catalyst, simple manipulation, and mild conditions.

Indene derivatives occupy a special place in organic and medicinal chemistry because of their important biological activities[1] and applications in functional materials.[2] Meanwhile, indene and its derivatives are also being extensively used as ligands in organometallics, especially for groups 4 and 10 metallocenes in the catalysis of olefin polymerization.[3] Consequently, a growing effort has been directed toward the development of new indene-based structures and new methods for their construction.[4] In recent years, some metal-catalyzed protocols have been well developed, such as rhenium-catalyzed annulation,[5] palladium-catalyzed carboannulation,[6] nickel- or cobalt-catalyzed carbocyclization,[7] and gold(I)-catalyzed intramolecular carboalkoxylation.[8] Moreover, Lewis acid-catalyzed ring expansion of substituted cyclopropanes and cyclopropenes,[9] and intramolecular hydroarylation of phenyl-substituted alkenes[10] have been well developed.

Catalytic substitution of the hydroxy group in alcohols with nucleophiles is an atom-efficient and environmentally sound transformation that is currently receiving considerable attention.[11] Although aryl-substituted allylic alcohols have been proved successfully to serve as precursors for synthesis of indenes via the intramolecular Friedel–Crafts reactions, in most cases a strong acidic medium and/or an excess amount of Lewis acid promoter is required.[12] To the best of our knowledge, only two examples have realized the Friedel–Crafts cyclization of allylic alcohols with a truly catalytic amount of Lewis acid catalysts.[12i,g] During our efforts to utilize allylic and propargylic alcohols as a practical and versatile alkylation reagent, we observed the formation of a 1,3-disubstituted indene in the presence of a catalytic amount of Lewis acids.[13] This has prompted us to develop a new shortcut method for synthesis of substituted indenes under mild reaction conditions.

On the other hand, iron salts attract considerable attention as a cheap replacement of the noble metal catalysts in many C–C bond formation reactions, owing to their outstanding advantages such as easy availability, low cost, low toxicity, environmental hospitality, and high activities.[14] In this contribution, we report that $FeCl_3·6H_2O$ can efficiently catalyze the intramolecular Friedel–Crafts reaction of aryl-substituted allylic alcohols to form indene derivatives.

Initially, 1,1,3-triphenylallyl alcohol **1a** was selected as a probe substrate. Treatment of **1a** with 5 mol % of $FeCl_3·6H_2O$ in toluene at 20 °C led to the occurrence of an isomerization/cyclization reaction, although the yield of the cyclization product **2a** was low (37% yield). To find a better reaction model system, various iron salt-based catalysts and different reaction conditions were tested, and the representative results are summarized in Table 1. It was found that when the reaction temperature was elevated to 40 °C, the yield increased to 81% within 1 h (Table 1, entry 2). The yield of **2a** was up to 91% if the reaction was performed under an argon atmosphere (Table 1, entry 3). Furthermore, other iron salts were also tested under similar reaction conditions. Anhydrous $FeCl_3$ exhibited a high activity for the present catalytic cyclization (Table 1, entry 7). However, $NH_4Fe(SO_4)_2·12H_2O$ and $FeCl_2·4H_2O$ as catalysts gave **2a** only in low yields (Table 1, entries 8 and 9). $Fe(acac)_3$ and $Fe(OAc)_2$ were inactive for the catalytic cyclization (Table 1, entries 10 and 11). $ZnCl_2$ as a catalyst was also explored for this process, and it exhibited low activity (Table 1, entry 12). Further investigation results demonstrated that the choice of solvents has a significant impact on the activity of the catalyst. The intramolecular Friedel–Crafts reaction also proceeded quite smoothly in 1,2-dichloroethane (DCE) (Table 1, entry 13). However, the replacement of toluene with polar solvents had a significantly negative effect on the intramolecular Friedel–Crafts reaction (Table 1, entries 14–16), especially in DMF the intramolecular Friedel–Crafts reaction did not proceed at all. In addition, either increasing or decreasing of the loading amount of the catalyst lowered the yields (Table 1, entries 5 and 6).

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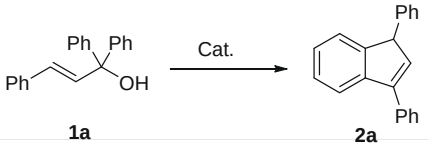
doi:10.1016/j.tetlet.2009.06.070

Table 1
The intramolecular Friedel–Crafts reaction of **1a** under various conditions[a]



1a **2a**

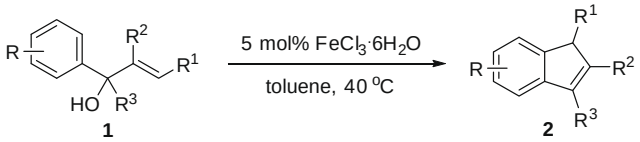
Entry	Cat. (mol %)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1[c]	$FeCl_3·6H_2O$ (5)	Toluene	20	2	37
2[c]	$FeCl_3·6H_2O$ (5)	Toluene	40	1	81
3	$FeCl_3·6H_2O$ (5)	Toluene	40	1	91
4	$FeCl_3·6H_2O$ (5)	Toluene	60	1	91
5	$FeCl_3·6H_2O$ (10)	Toluene	40	1	89
6	$FeCl_3·6H_2O$ (1)	Toluene	40	2	75
7	$FeCl_3$ (5)	Toluene	40	1	90
8	$NH_4Fe(SO_4)_2·12H_2O$ (5)	Toluene	40	1	14
9	$FeCl_2·4H_2O$ (5)	Toluene	40	1	18
10	$Fe(acac)_3$ (5)	Toluene	40	1	0
11	$Fe(OAc)_2$ (5)	Toluene	40	1	0
12	$ZnCl_2$ (5)	Toluene	40	1	18
13	$FeCl_3·6H_2O$ (5)	DCE	40	1	90
14	$FeCl_3·6H_2O$ (5)	THF	40	2	14
15	$FeCl_3·6H_2O$ (5)	CH_3CN	40	2	39
16	$FeCl_3·6H_2O$ (5)	DMF	40	2	0

[a] Reaction conditions: **1a** (0.5 mmol), solvent (1 mL) and catalyst under an argon atmosphere.
[b] Isolated yield.
[c] The reactions were carried out in air atmosphere.

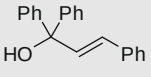
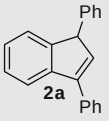
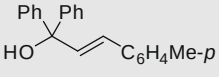
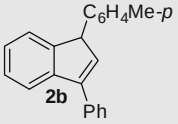
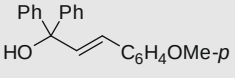
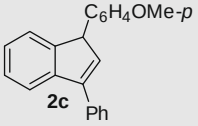
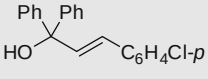
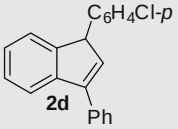
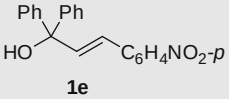
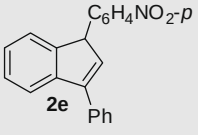
With the optimum reaction conditions in hand, we subsequently explored the scope of the reaction for various allylic alcohols bearing aryl ring moiety.[14,15] As shown in Table 2, all the allylic alcohols examined smoothly cyclized to the corresponding indenes in moderate to high yields with perfect regioselectivity. In contrast to the previous observation in other Lewis acid-catalyzed intramolecular Friedel–Crafts reactions, wherein the electrocyclic ring closure to indenes took place at the allylic position regioselectively, the present cyclization preferentially proceeded from the least substituted end of the allylic system through isomerization process (Scheme 1), irrespective of the electronic nature of aryl rings at both ends of the allylic system (Table 2, entries 2–6, 10–11). The complete absence of indene **6a** in the reaction mixture might be partly attributed to the large steric hindrance at the allylic position (Scheme 1).

The substituent effect on the allylic position was also investigated. Phenyl-, aryl-, and alkyl-disubstituted substrates were all compatible with the cyclization conditions, and gave the corresponding indenes in high yields (Table 2, entries 1–11). There were no significant differences in reactivity and selectivity between the allylic alcohols with or without a methyl group at *2*-position (Table 2, entries 1 and 7). Moreover, secondary allylic alcohols **1l** and **1m** could also undergo the intramolecular Friedel–Crafts reaction to afford the desired products (Table 2, entries 12 and 13). It should be noted that the selectivity of the cyclization could be easily controlled by the electronic effect of the aryl groups, when the steric hindrance at the 1-position of allylic cations is comparable to that

Table 2
$FeCl_3·6H_2O$-catalyzed intramolecular Friedel–Crafts reaction of allylic alcohols[a]

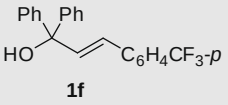
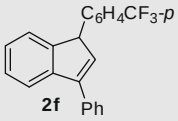
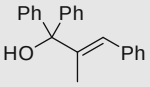
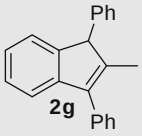
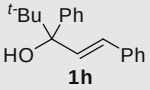
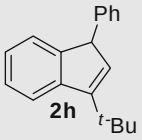
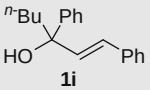
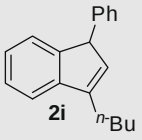
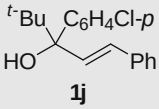
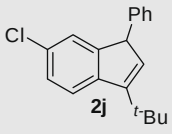
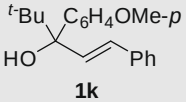
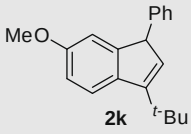
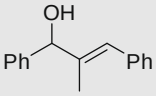
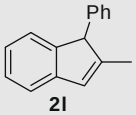
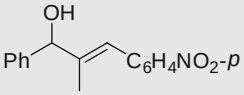
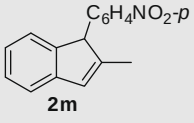
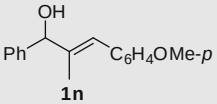
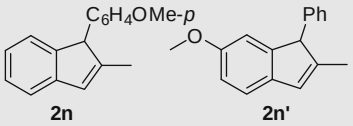
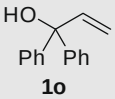
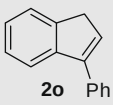
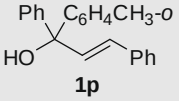
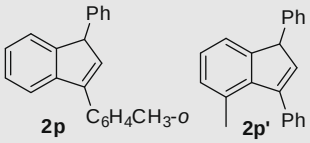


1 **2**

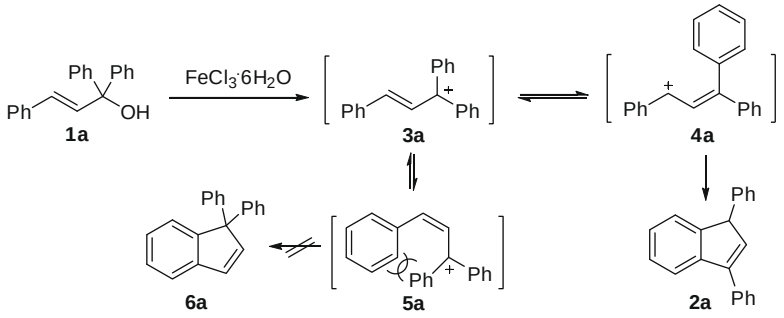
Entry	Substrate	Time (h)	Product	Yield[b] (%)
1	 **1a**	1	 **2a**	91
2	 **1b**	1	 **2b**	88
3	 **1c**	1	 **2c**	89
4	 **1d**	1	 **2d**	86
5	 **1e**	1	 **2e**	89

(*continued on next page*)

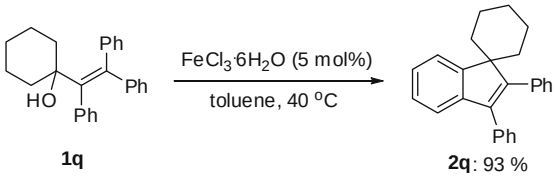
Table 2 (*continued*)

Entry	Substrate	Time (h)	Product	Yield[b] (%)
6	 **1f**	2	 **2f**	82
7	 **1g**	1	 **2g**	87
8	 **1h**	1	 **2h**	90
9	 **1i**	1	 **2i**	84
10	 **1j**	1	 **2j**	91
11	 **1k**	1	 **2k**	88
12	 **1l**	1	 **2l**	90
13	 **1m**	2	 **2m**	70
14[c]	 **1n**	1	 **2n** **2n'**	88
15[d]	 **1o**	2	 **2o**	56
16	 **1p**	2	 **2p** **2p'**	88

[a] Reaction conditions: allylic alcohol (0.50 mmol) and $FeCl_3{\cdot}6H_2O$ (0.025 mmol) in toluene (1 mL) at 40 °C under an argon atmosphere.
[b] Isolated yield.
[c] The ratio of **2n**/**2n**′ is 2:1.
[d] 10 mol % $FeCl_3{\cdot}6H_2O$ was used.



Scheme 1.



Scheme 2.

at the 3-position. For example, treatment of **1m** with 5 mol % $FeCl_3$ gave only **2m** (Table 2, entry 13), while **1n** formed a 2:1 mixture of **2n** and **2n′** under the same conditions (Table 2, entry 14). These results indicate that the selectivity would favor the allylic cation which is most stabilized to effect electrophilic attack unless the nucleophilic benzene ring has a strong electron-deficient substituent (such as nitro). In addition, it was found that the introduction of either the electron-donating or weak electron-withdrawing (e.g., chloro) group at the *para*-position of the nucleophilic benzene ring had only a slight influence on the reactivity compared with those without a substituent on the aromatic ring (Table 2, entries 10 and 11). An alcohol **1o** could also be applied in this reaction to form compound **2o** in 56% yield (Table 2, entry 15). The results described above clearly demonstrate that, in the present catalytic system, the different types and numbers of substituents on the indene skeleton could be controlled by applying allylic alcohols bearing the desired types and numbers of substituents. The allylic alcohol without a hydrogen at carbon–carbon double bond positions (**1q**) used as a substrate also gave the cyclization product in high yield (Scheme 2).

In summary, an experimentally convenient, efficient, and cheap catalytic process for the synthesis of substituted indenes from aryl-substituted allylic alcohols via an intramolecular Friedel–Crafts reaction has been established. Significant substrate flexibility and excellent control of the double bonds and substituent position render this an attractive method for the synthesis of versatile substituted indenes.

Acknowledgments

We thank the NNSF of China, 973 program (2009CB825300), NSF of Shanghai, and Shanghai Leading Academic Discipline Project for financial support (B108).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.070.

References and notes

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15. *General procedure*: To allylic alcohol **1** (0.5 mmol) in toluene (1 mL) was added $FeCl_3·6H_2O$ (6.7 mg, 0.025 mmol) under an argon atmosphere and then the reaction mixture was stirred at 40 °C for 1 h. After completion of the reaction, the mixture was quenched with water and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and dried over Na_2SO_4. After

filtration and removal of the solvent in vacuo, the crude product was purified by flash chromatography using ethyl acetate/petroleum ether (V/V: 1/50) as eluent. 1,3-*Diphenylindene* (**2a**): ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.10–7.65 (m, 14H), 6.63 (d, J = 1.8 Hz, 1H), 4.70 (d, J = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ 149.4, 144.7, 143.3, 139.6, 136.4, 135.7, 128.8, 128.7, 128.1, 127.9, 127.8, 127.0, 126.8, 125.7, 124.4, 120.7, 55.5. MS (EI) m/z: 268 (100) [M^+].