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Intramolecular electrophilic aromatic substitution of α-alkylcinnamaldehydes affording 1-alkoxy-2-alkylindenes

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Abstract—Treatment of α-alkylcinnamaldehydes with orthoesters, alcohols, or thiols in the presence of $BF_3{\cdot}OEt_2$ induces an intramolecular electrophilic aromatic substitution reaction to afford 1-alkoxy-2-alkylindenes. The reaction mechanisms of the indene formation have been elucidated on the basis of the reaction behaviors of β-deuterated α-methylcinnamaldehyde and the NMR studies of the reaction mixture. The transformation process involves successive reactions, i.e., alkoxylation of the carbonyl carbon of α-alkylcinnamaldehydes to form acetals, elimination of alkoxide from the acetals to give alkoxycarbenium ion and γ-alkoxyallyl cation, and intramolecular electrophilic arylation to afford the indene ring structure.

1. Introduction

Indene derivatives are frequently found in natural products and widely employed as medicinal compounds.[1–5] In accordance with this, indene derivatives have attracted organic and pharmaceutical chemists. One of the conventional approaches toward producing the indene framework is acid-mediated cyclodehydration reaction of aryl ketones.[6–8] Some 1-phenylallyl cations also undergo the intramolecular cyclization to afford the corresponding indenes.[9–12] In these cases, the cyclization proceeds via electrophilic aromatic substitution mechanisms. While various substituted indenes have so far been prepared by these methods, synthesis of 1-indenols and 1-alkoxyindenes through the electrophilic aromatic substitution process has not been reported. Recently, transition metal catalyzed coupling reactions of alkynes with *ortho*-carbonylated arylhalides[13] or arylboron compounds[14] have been developed as an effective method for the preparation of 1-indenols. The transition metal catalyzed annulation reaction has also been applied for the construction of indenes.[15,16] Nevertheless, an efficient and practical means to construct 1-alkoxyindene frameworks has been an ongoing challenge. Almost all of the syntheses of 1-alkoxyindenes are performed via multi step transformations[5,17] or low chemoselective one-pot preparations,[18] except for a recent report of Pd-complex catalyzed intramolecular cyclization of alkynylbenzaldehyde dialkyl acetals to form dialkoxyindenes.[19]

During the study on the acid mediated oxidative crossed aldol type reaction of aliphatic ethers with benzaldehyde dimethyl acetal giving α,β-unsaturated carbonyl compounds,[20] we have found that several ethers afford 1-alkoxy-2-alkylindenes in place of α,β-unsaturated carbonyl compounds.[21] Our preliminary study indicated that the produced α,β-unsaturated carbonyl compounds may be further transformed to 1-alkoxy-2-alkylindenes during the reaction.

In consequence, we have investigated the above reaction aiming at the development of the efficient one-pot synthesis of 1-alkoxyindenes to reveal the structural requirements and the activation process. In this paper, the reaction features, the scope and limitations, and the reaction mechanisms of the transformation of α-alkylcinnamaldehydes into 1-alkoxyindenes are discussed.

2. Results and discussion

2.1. The reaction behaviors and characterization of the products

We have recently reported that the BF_3 mediated reaction of bis(β-alkylethyl) ethers with benzaldehyde dimethyl acetal

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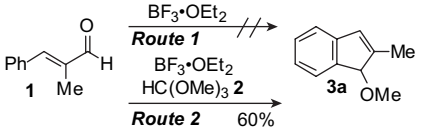
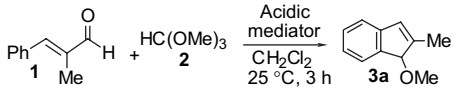
affords 1-alkoxy-2-alkylindenes.[21] As some kinds of aliphatic ethers yield α,β-unsaturated carbonyl compounds in the presence of benzaldehyde dimethyl acetal and BF_3 etherates, α,β-unsaturated carbonyl compounds were obviously regarded as the precursors for the 1-alkoxyindene formation reaction.[20,21] However, the treatment of $BF_3{\cdot}OEt_2$ against α-methylcinnamaldehyde (**1**) did not afford any indenes (Scheme 1, Route 1). In this case, aldehyde **1** was recovered. In contrast, addition of trimethyl orthoformate [$HC(OMe)_3$ (**2**)] to this reaction system has been found to accomplish the transformation affording 1-methoxy-2-methylindene (**3a**) in a good yield (Scheme 1, Route 2). These facts demonstrate that α-methylcinnamaldehyde (**1**) by itself is not the direct precursor of 1-methoxyindene **3a**, but has a capability to form 1-methoxy-2-methylindene (**3a**) with the aid of $HC(OMe)_3$ (**2**).



Scheme 1.

Table 1 shows the results of the reaction of α-methylcinnamaldehyde (**1**) with $HC(OMe)_3$ (**2**) in the presence of several acidic mediators.

Table 1. Reaction of α-methylcinnamaldehyde (**1**) with $HC(OMe)_3$ (**2**) in the presence of several acidic mediators[a]



Entry	**2**/**1** (mol/mol)	Acidic mediator	Acidic mediaor/**1** (mol/mol)	NMR yield/%[b]
1	1	$BF_3{\cdot}OEt_2$	1	60
2	2	$BF_3{\cdot}OEt_2$	1	72
3	4	$BF_3{\cdot}OEt_2$	1	79
4	4	$BF_3{\cdot}OEt_2$	0.5	37
5	4	$BF_3{\cdot}OEt_2$	2	74
6	4	$BF_3{\cdot}OMe_2$	1	57
7	4	$AlCl_3$	1	8
8	4	$SnCl_4$	1	5
9	4	$ZnCl_2$	1	32
10	4	H_2SO_4	1	35
11	4	CF_3SO_3H	1	68

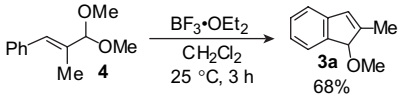
[a] Reaction conditions: α-methylcinnamaldehyde (**1**), 0.5 mmol; CH_2Cl_2, 2.5 mL; 25 °C, 3 h.
[b] Determined by ^1H NMR spectrum with the use of nitrobenzene as internal standard.

In the presence of one equimolar amount of $BF_3{\cdot}OEt_2$, the treatment of α-methylcinnamaldehyde (**1**) with four equimolar amounts of $HC(OMe)_3$ (**2**) afforded 1-methoxyindene **3a** in a high yield (79%, Entry 3). However, the reaction was retarded with the decrease in the amount of $HC(OMe)_3$ (**2**) (Entries 1 and 2). In addition, the use of catalytic amount of $BF_3{\cdot}OEt_2$ resulted in a lower yield of 1-methoxyindene **3a** (Entry 4), while the treatment with excess amount of $BF_3{\cdot}OEt_2$ afforded 1-methoxyindene **3a** in a comparative yield (Entry 5).

Among the acidic mediators employed, $BF_3{\cdot}OEt_2$ afforded 1-methoxy-2-methylindene (**3a**) in the highest yield (Entry 3). Acidic mediators except $BF_3{\cdot}OEt_2$ gave aldehyde **1** and/or unidentified products that have broad signals of aromatic ring protons and alkyl group ones in ^1H NMR spectra (Entries 6–10), though triflic acid also gave 1-methoxyindene **3a** in a good yield (Entry 11). These by-products are probably composed of some kinds of polymeric compounds formed via cationic polymerization of 1-alkoxyindene[22] and/or α-methylcinnamaldehyde (**1**)[23] produced in the early stage of the reaction.

2.2. Effect of the alkoxylating agent

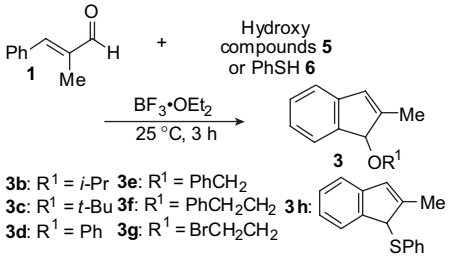
Generally, treatment of orthoester against aldehyde in the presence of acidic mediator is known to give acetal.[24] In other words, acetals of α-alkylcinnamaldehydes were considered to be the actual precursors of the 1-alkoxyindenes in this transformation. In fact, when α-methylcinnamaldehyde dimethyl acetal (**4**) was treated with $BF_3{\cdot}OEt_2$ in the absence of $HC(OMe)_3$ (**2**), 1-methoxy-2-methylindene (**3a**) was also formed in a good yield (Scheme 2). Therefore, 1-alkoxyindenes must be produced via the acetal of α-alkylcinnamaldehyde or at least its equivalent.



Scheme 2.

Acetals are also synthesized by the reaction of aldehyde with alcohol or thiol.[24] Therefore, alcohols and thiols are expected to react with aldehyde **1** affording the corresponding indenes. Table 2 shows the results of the reaction using other hydroxy compounds **5** or thiophenol (**6**). When MeOH (**5a**)

Table 2. Reaction of α-methylcinnamaldehyde (**1**) with hydroxy compounds **5** or thiophenol (**6**) in the presence of $BF_3{\cdot}OEt_2$[a]



Entry	**5** or **6**	**5** or **6**/**1** (mol/mol)	$BF_3{\cdot}OEt_2$/**1** (mol/mol)	**3**	NMR yield/%[b]
1[c]	MeOH **5a**	4	1	**3a**	Trace
2	**5a**	10	10	**3a**	69
3	*i*-PrOH **5b**	10	10	**3b**	54
4	*t*-BuOH **5c**	10	10	**3c**	0
5	PhOH **5d**	10	10	**3d**	0
6	$PhCH_2OH$ **5e**	10	10	**3e**	0
7	$PhCH_2CH_2OH$ **5f**	10	10	**3f**	56
8	$BrCH_2CH_2OH$ **5g**	10	10	**3g**	30
9	PhSH **6**	10	10	**3h**	59

[a] Reaction conditions: aldehyde **1**, 0.5 mmol; 25 °C, 3 h.
[b] Determined by ^1H NMR spectrum with the use of nitrobenzene as internal standard.
[c] Reaction conditions: aldehyde **1**, 0.5 mmol; CH_2Cl_2, 2.5 mL; 25 °C, 3 h.