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Facile synthesis of dihydrochalcones via the $AlCl_3$-promoted tandem Friedel–Crafts acylation and alkylation of arenes with 2-alkenoyl chlorides

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ABSTRACT

Tandem Friedel–Crafts acylation and alkylation of arenes with 2-alkenoyl chlorides were investigated under the catalysis of Lewis acids. The cascade reaction affords dihydrochalcones in good yields accompanying 1-indanone derivatives in some cases, in the presence of anhydrous aluminum chloride. The scope, limitation, and mechanism of the tandem reaction were also explored. The intermolecular Friedel–Crafts alkylation for the formation of dihydrochalcones is more favorable than the intramolecular one for the generation of 1-indanones in the tandem reaction due to a stable six-membered ring transition state. The sequent process was further studied by the DFT computations at the M06-2X/6-31G(d) level, which are in great agreement with the experimental observation and support the proposed mechanism. The current method provides a convenient and economic method to synthesis of dihydrochalcones.

1. Introduction

Friedel–Crafts acylation and alkylation are powerful and convenient methods for the preparation of acyl and alkyl substituted arenes, respectively [1]. Tandem reactions have attracted much attention and have been used widely in synthetic organic chemistry during recent two decades due to their high efficiency and diversity [2,3]. It was reported that the reaction of benzaldehyde and benzene produced diphenylmethanol, which further yielded triphenylmethane under the catalysis of anhydrous aluminum chloride [4]. This is an early example of tandem Friedel–Crafts alkylations. Both aromatic and aliphatic aldehydes underwent the tandem Friedel–Crafts alkylation with electron-rich arenes to afford 1,1,1-triaryl/1,1-diarylalkanes in the presence of anhydrous aluminum chloride under solvent-free conditions [5]. $LnCl_3$ (Ln = Pr, Dy, Er, Sm, Yb) and $Yb(O_3SCF_3)_3$ catalyzed alkylation of PhR (R = H, Me) with AcCl–PhCHO to give $PhCH(CH_6H_4R)_2$ was also reported [6]. Strong proton acid-catalyzed tandem Friedel–Crafts reactions of arenes with aromatic aldehydes have been investigated as well [7]. Recently we discovered the tandem Friedel–Crafts acylation and alkylation of arenes with acyl chlorides and α,β-unsaturated acyl chlorides in the presence of anhydrous aluminum chloride, to afford 1,1-diaryl-1-alkenes and indanone derivatives in good yields, respectively [8]. Tandem reactions of α,β-unsaturated acyl chlorides with phenols have also been carried out to synthesize dihydrocoumarins [9]. A copper(II) triflate-catalyzed tandem Friedel–Crafts alkylation/cyclization process was developed to prepare dihydroindenes [10]. Indenoindene-fused α-methylene-γ-butyrolactones were synthesized via a tandem intra- and intermolecular Friedel–Crafts reaction [11]. The TFA-mediated tandem Friedel–Crafts alkylation/cyclization/hydrogen transfer process has been explored to provide an efficient approach to the synthesis of flavylium compounds from chalcones and phenols [12]. When this article was revised, the superacid catalyzed synthesis of trifluoromethylated dihydrochalcones, aryl vinyl ketones, and indanones from arenes and 4,4,4-trifluoro/3-(trifluoromethyl)crotonic acids was reported [13].

To further extend the application of the tandem Friedel–Crafts acylation and alkylation of arenes with α,β-unsaturated acyl chlorides under the catalysis of Lewis acids (LAs), we systematically studied the reaction to prepare dihydrochalcone derivatives, which are important intermediates in organic and pharmaceutical syntheses [14]. Dihydrochalcone derivatives have been prepared previously via the selective catalytic hydrogenation of chalcones [15], via coupling of acetophenone and benzyl alcohol [16], via coupling of cinnamaldehyde and aryl halides, [17] and via the Suzuki cross-coupling of 3-phenylpropanoyl chloride [18] or cinnamaldehyde [19] and phenylboronic acid, in which noble metals were employed as catalysts and/or the reactions were conducted under high pressure. Herein, we wish to report a facile synthesis of dihydrochalcones via the $AlCl_3$-promoted tandem Friedel–Crafts

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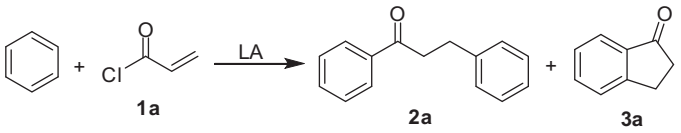
Table 1
Tandem Friedel–Crafts acylation and alkylation of acryloyl chloride with benzene.[a]



Entry	LA	LA (equiv.)	Benzene (mL)	Temp. (°C)	Addition time	Reaction time	Isolated yield (%)	
							2a	**3a**
1	BF_3 OEt_2	1.5	15	25–30		48 h	–	–
2	$ZnCl_2$	0.5	15	25–30		5 h	–	–
3	$ZnCl_2$	1.0	15	25–30		12 h	–	–
4	$ZnCl_2$	1.0	9	Reflux		72 h	Trace	–
5	$AlCl_3$	1.2	3	25–30		1 h	14[b]	20[b]
6	$AlCl_3$	1.5	25	25–30	1 h	1 h	52	12
7	$AlCl_3$	1.2	9	Reflux	20 min	1 h	35[b]	15[b]
8	$AlCl_3$	1.2	10	Reflux	1 h	20 min	69	Trace
9	$AlCl_3$	1.5	15	Reflux	3.3 h	20 min	81	Trace

[a] A solution of acryloyl chloride (0.95 g, 10 mmol) in benzene (8 mL) was added in a suspension of Lewis acid in benzene.
[b] Yield obtained from ^{1}H MNR analysis of a mixture of isolated products **2a** and **3a**.

acylation and alkylation of arenes with 2-alkenoyl chlorides and to discuss its scope, limitation, and mechanism.

2. Experimental

General methods. Melting points were measured on a Yanaco MP–500 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 (400 MHz) spectrometer in $CDCl_3$ with TMS as an internal standard.

General procedure for the $AlCl_3$-promoted tandem Friedel–Crafts acylation and alkylation of arenes with 2-alkenoyl chlorides. To a stirring mixture of anhydrous aluminum chloride (2.0 g, 15 mmol) and arene (15 mL for the reaction under refluxing, 25 mL for the reaction at RT) was added a solution of 2-alkenoyl chloride (10 mmol) in the same arene (8 mL) dropwise during 3 h at 25–30 °C (RT) or under refluxing. After addition, the resulting mixture was kept stirring for 20 min and then allowed to cool to the room temperature. It was poured into 150 mL of 1 mol/L HCl to decompose $AlCl_3$ complex. After phase separation, the aqueous phase was extracted with ethyl acetate (3× 50 mL). After dried over Na_2SO_4 and evaporation of the solvents, the residue was purified on silica gel column with a mixture of petroleum ether (60–90 °C) and ethyl acetate (10:1, *v/v*) as eluent to afford the desired product.

*1,3-Diphenylpropan-1-one (**2a**)*. Colorless crystals, m.p. 72–73 °C (Lit. [20] m.p. 74–75 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.07 (t, J = 7.7 Hz, 2H, CH_2), 3.30 (t, J = 7.7 Hz, 2H, CH_2), 7.19–7.32 (m, 5H, ArH), 7.43–7.47 (m, 2H, ArH), 7.53–7.57 (m, 1H, ArH), 7.96 (d, J = 8.2 Hz, 2H, ArH).

*1-Indanone (**3a**)*. Colorless crystals, m.p. 39–42 °C (Lit. [21] m.p. 39–41 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.68 (t, J = 6.0 Hz, 2H, CH_2), 3.14 (t, J = 6.0 Hz, 2H, CH_2), 7.34–7.38 (t, J = 7.42 Hz, 1H, ArH), 7.46–7.48 (d, J = 7.6 Hz, 1H, ArH), 7.56–7.60 (t, J = 7.42 Hz, 1H, ArH), 7.74–7.76 (d, J = 7.64 Hz, 1H, ArH).

*1,3-Diphenylbutan-1-one (**2b**)* [22]. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J = 6.9 Hz, 3H, CH_3), 3.19 (dd, J = 8.3, 16.4 Hz, 1H in CH_2), 3.30 (dd, J = 5.7, 16.4 Hz, 1H in CH_2), 3.49–3.62 (m, 1H, CH), 7.18–7.35 (m, 5H, ArH), 7.42–7.50 (m, 2H, ArH), 7.52–7.60 (m, 1H, ArH), 7.93–7.97 (m, 2H, ArH).

*3-Methyl-1-indanone (**3b**)* [8b]. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (d, J = 7.1 Hz, 3H, CH_3), 2.28 (dd, J = 3.5, 19.0 Hz, 1H in CH), 2.94 (dd, J = 7.5, 19.0 Hz, 1H in CH), 3.40–3.48 (m, 1H, CH), 7.37 (t, J = 7.4, 1H, ArH), 7.51 (d, J = 7.7 Hz, 1H, ArH), 7.61 (t, J = 7.4, 1H, ArH), 7.73 (d, J = 7.7, 1H, ArH).

*3-Methyl-1,3-diphenylbutan-1-one (**2c**)* [23]. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (s, 6H, $2CH_3$), 3.30 (s, 2H, CH_2), 7.13–7.17 (m, 1H, ArH), 7.24–7.29 (m, 2H, ArH), 7.35–7.38 (m, 4H, ArH), 7.42–7.53 (m, 2H, ArH), 7.80–7.82 (m, 2H, ArH).

*3,3-Dimethyl-1-indanone (**3c**)* [24]. Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 6H, $2CH_3$), 2.59 (s, 2H, CH_2), 7.35–7.39 (m, 1H, ArH), 7.49–7.51 (m, 1H, ArH), 7.60–7.64 (m, 1H, ArH), 7.69–7.71 (m, 1H, ArH).

*1,3,3-Triphenylpropan-1-one (**2d**)* [25]. White solid, m.p. 93 °C, (Lit. m.p. 88 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (d, J = 7.3 Hz, 2H, CH_2), 4.83 (t, J = 7.3 Hz, 1H, CH), 7.15–7.20 (m, 2H, ArH), 7.25–7.27 (m, 8H, ArH), 7.42–7.45 (m, 2H, ArH), 7.52–7.57 (m, 1H, ArH), 7.92–7.94 (m, 2H, ArH).

*2-Methyl-1,3-diphenylpropan-1-one (**2e**)* [26]. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (d, J = 6.9 Hz, 3H, CH_3), 2.69 (dd, J = 7.9, 13.7 Hz, 1H in CH), 3.17 (dd, J = 6.3, 13.7 Hz, 1H in CH), 3.70–3.79 (m, 1H, CH), 7.15–7.20 (m, 3H, ArH), 7.24–7.28 (m, 2H, ArH), 7.42–7.46 (m, 2H, ArH), 7.51–7.56 (m, 1H, ArH), 7.91–7.93 (m, 2H, ArH).

*2-Methyl-1-indanone (**3e**)* [27]. Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (d, J = 7.3 Hz, 3H, CH_3), 2.67–2.76 (m, 2H, CH_2), 3.40 (dd, J = 8.8, 17.9 Hz, 1H, CH), 7.37 (t, J = 7.4 Hz, 1H, ArH), 7.45 (d, J = 7.7 Hz, 1H, ArH), 7.58 (dt, J = 7.4, 1.2 Hz, 1H, ArH), 7.76 (d, J = 7.7 Hz, 1H, ArH).

*1,3-Di(-p-tolylpropan-)1-one (**2g**)* and its isomers, light yellow oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.32–2.41 (m, 6H, $2CH_3$), 3.00–3.06 (m, 2H, CH_2), 3.20–3.27 (m, 2H, CH_2), 7.09–7.19 (m, 4H, ArH), 7.23–7.26 (m, 2H, ArH), 7.84–7.88 (m, 2H, ArH).

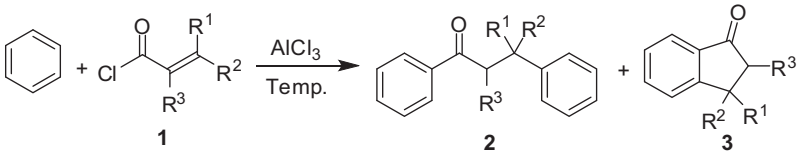
*3-Methyl-1,3-di(-p-tolylbutan-)1-one (**2h**)* and its isomers, light yellow oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.46–1.47 (m, 6H, $2CH_3$), 2.27–2.37 (m, 6H, $2CH_3$), 3.21–3.25 (m, 2H, CH_2), 7.05–7.28 (m, 6H, ArH), 7.72–7.75 (m, 2H, ArH).

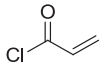
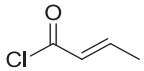
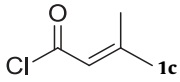
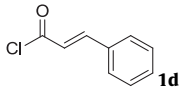
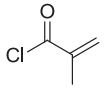
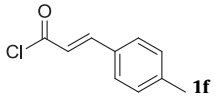
*1,3,3-Tri(-p-tolylpropan-)1-one (**2i**)* and its isomers, colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.26–2.28, (m, 6H, $2CH_3$), 2.38 (s, 3H, CH_3), 3.65–3.68 (m, 2H, CH_2), 4.72–4.75 (m, 1H, CH), 6.95–6.97 (m, 1H, CH), 7.05–7.07 (m, 4H, ArH), 7.12–7.15 (m, 3H, ArH), 7.20–7.22 (m, 2H, ArH), 7.82–7.84 (m, 2H, ArH).

*1,3-Dimesitylpropan-1-one (**2j**)* [28]. Colorless crystals, m.p. 80–82 °C (Lit. m.p. 80–81 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 6H), 2.24 (s, 3H), 2.26 (s, 3H), 2.28 (s, 6H), 2.80 (t, J = 8.0 Hz, 2H), 3.02 (t, J = 8.0 Hz, 2H), 6.82 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 19.6, 20.8, 21.0, 23.1, 43.9, 128.5, 129.0, 132.3, 134.4, 135.4, 135.8, 138.3, 139.5, 210.3. HRMS (ESI) *m/z*: Calcd for $C_{21}H_{27}O$: 295.2056; Found: 295.2053.

*(E)-1-Mesitylbut-2-en-1-one (**5b**)* [29]. Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90 (d, J = 6.8 Hz, 3H), 2.21 (s, 6H), 2.28 (s, 3H), 6.31 (d, J = 15.6 Hz, 1H), 6.50 (dq, J = 15.6 and 6.8 Hz, 1H), 6.83 (s, 2H).

Table 2
Tandem Friedel–Crafts acylation and alkylation of 2-alkenoyl chlorides with benzene.[a]



Entry	2-Alkenoyl chloride	Temp. (°C)	Isolated yield (%)	
			2	**3**
1	 **1a**	Reflux	81	Trace
2		30	52	12
3	 **1b**	Reflux	21[b]	39[b]
4		30	Trace	Trace
5		55	35[b]	12[b]
6	 **1c**	Reflux	40	38
7		30	77	–
8	 **1d**	Reflux	50	–
9		30	63	Trace
10	 **1e**	Reflux	21[b]	74[b]
11		30	34	19
12	 **1f**	Reflux	65 (**2d**)	–
13		30	67 (**2d**)	–

[a] A solution of 2-alkenoyl chloride (10 mmol) in benzene (8 mL) was added dropwise slowly in a suspension of aluminum chloride (2.0 g, 15 mmol) in benzene (15 mL) under refluxing during 3.3 h. The resulting solution was further stirred for 20 min. Or a solution of 2-alkenoyl chloride (10 mmol) in benzene (8 mL) was added dropwise slowly in a suspension of aluminum chloride (2.0 g, 15 mmol) in benzene (25 mL) at 25–30 °C (for acyl chloride **1b** at 55 °C) during 3.3 h. The resulting solution was further stirred for 1 h.
[b] Yield obtained from ^{1}H MNR analysis of a mixture of isolated products **2** and **3**.

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 19.2, 21.0, 128.2, 133.8, 134.1, 137.2, 138.1, 147.8, 201.5.

*1-Mesityl-3-methylbut-2-en-1-one (**5c**)* [29b]. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.09 (s, 3H), 2.19 (s, 6H), 2.27 (s, 3H), 6.22 (s, 1H), 6.82 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 20.5, 21.0, 28.0, 126.4, 128.4, 133.1, 137.9, 140.4, 156.1, 199.8.

*(E)-1-Mesityl-3-phenylprop-2-en-1-one (**5d**)* [30]. Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19 (s, 6H), 2.32 (s, 3H), 6.89 (s, 2H), 6.93 (d, J = 16.4 Hz, 1H), 7.19 (d, J = 16.4 Hz, 1H), 7.36–7.39 (m, 3H, ArH), 7.49–7.52 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 21.1, 128.4, 128.4, 128.5, 129.0, 130.8, 134.1, 134.5, 137.1, 138.3, 146.7, 201.4.

*(E)-1-(2,5-Dimethylphenyl)but-2-en-1-one (**5e**)* [31]. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94 (dd, J = 6.8 and 1.6 Hz, 3H), 2.32 (s, 3H), 2.33 (s, 3H), 6.52 (dd, J = 15.6 and 1.6 Hz, 1H), 6.74 (dq, J = 15.6 and 6.8 Hz, 1H), 7.09–7.15 (m, 2H), 7.17 (s, 1H).

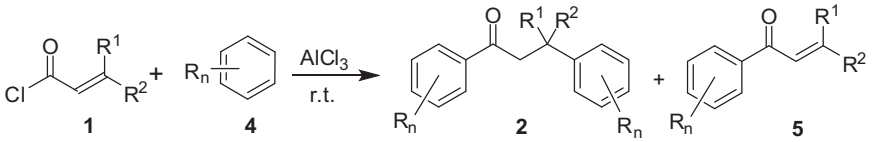
3. Calculational method

All calculations were performed with Gaussian 09 [32]. The M06-2X level [33] with the 6-31G(d,p) basis set [34] was applied for the optimization of all the stationary points in the gas phase. Frequency calculations were performed at the M06-2X level to confirm that each stationary point is either a minimum or a transition structure, which is confirmed by the vibrational analysis and characterized by only one imaginary vibrational mode. Solvation energies were evaluated by a self-consistent reaction field (SCRF) using the CPCM model, [35] where UFF radii were used. Solvation calculations were carried out at M06-2X level on the gas-phase optimized structures. The reported energies are zero-point energy-corrected Gibbs free energies in benzene solution (ΔG_{sol}).

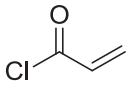
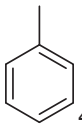
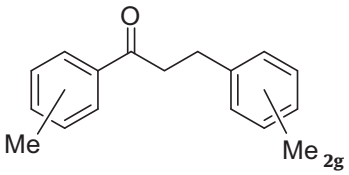
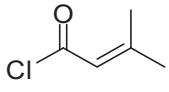
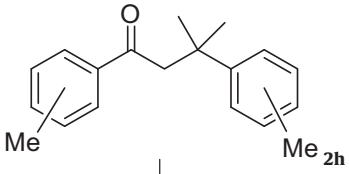
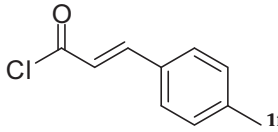
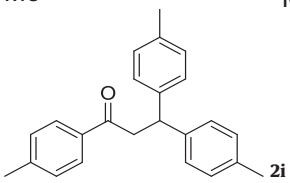
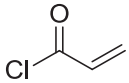
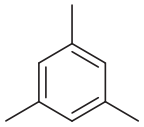
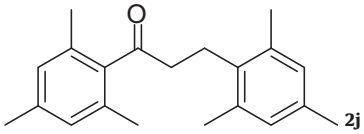
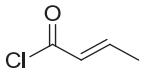
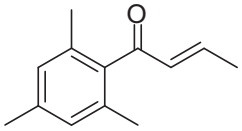
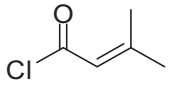
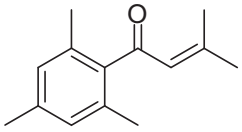
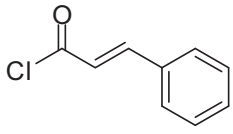
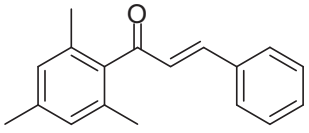
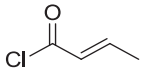
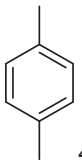
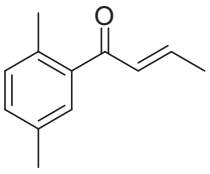
4. Results and discussion

The tandem Friedel–Crafts acylation and alkylation of equivalent arenes and 2-alkenoyl chlorides have been successfully used to prepare indanone derivatives. The tandem reaction includes Friedel–Crafts acylation of arenes with 2-alkenoyl chlorides and subsequent intramolecular Friedel–Crafts alkylation or the Nazarov cyclization [8b]. Additionally, Olah and his co-workers reported that acrylic acid reacted with equivalent benzene in dichloromethane to give rise to a mixture of 1-indanone and dihydrochalcone under the catalysis of superacidic acid trifluoromethanesulfonic acid when they investigated the superacidic trifluoromethanesulfonic acid-induced synthesis of 1-indanone and 1-tetralone derivatives through the Friedel–Crafts cycliacylalkylation of aromatics with unsaturated carboxylic acids [36]. These inspire us to attempt to synthesize dihydrochalcone derivatives via intermolecular tandem Friedel–Crafts acylation and alkylation of arenes with 2-alkenoyl chlorides under the catalysis

Table 3
Tandem Friedel–Crafts acylation and alkylation of 2-alkenoyl chlorides with arenes.[a]

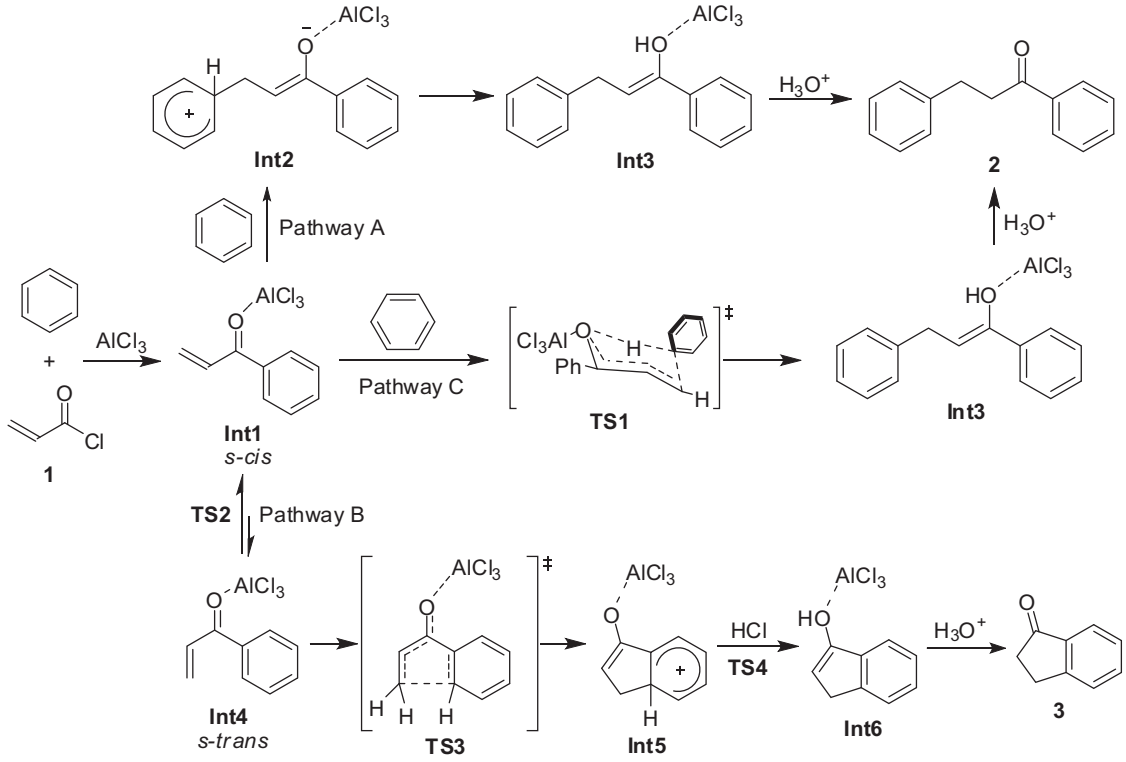


1 4 2 5

Entry	2-Alkenoyl chloride 1	ArH **4**	**2** or **5**	**2** or **5** yield (%)
1	 **1a**	 **4a**	 **2g**	88
2	 **1c**	**4a**	 **2h**	83
3	 **1f**	**4a**	 **2i**	61
4	 **1a**	 **4b**	 **2j**	90
5	 **1b**	**4b**	 **5b**	83
6	 **1c**	**4b**	 **5c**	93
7	 **1d**	**4b**	 **5d**	85
8	 **1b**	 **4c**	 **5e**	65

[a] A solution of 2-alkenoyl chloride (10 mmol) in arene (8 mL) was added dropwise slowly in a suspension of aluminum chloride (2.0 g, 15 mmol) in arene (25 mL) at 25–30 °C during 3 h. The resulting solution was further stirred for 1 h.

of Lewis acids. We envisioned that the synthesis could be realized if the corresponding arenes were used in an excessive amount, such as a solvent. We firstly used the reaction of acryloyl chloride (**1a**) and benzene as a model reaction to optimize the reaction conditions. To keep a high ratio of benzene:acryloyl chloride during the whole reaction period, a solution of acryloyl chloride (**1a**) in benzene was added dropwise slowly into benzene in the presence of different Lewis acids. The results are summarized in Table 1. It can be seen that no reaction occurred under the catalysis of either boron trifluoride or zinc chloride (Table 1, entries 1–4). However,



Scheme 1. Proposed mechanism for the $AlCl_3$-promoted tandem Friedel–Crafts acylation and alkylation of arenes with 2-alkenoyl chlorides.

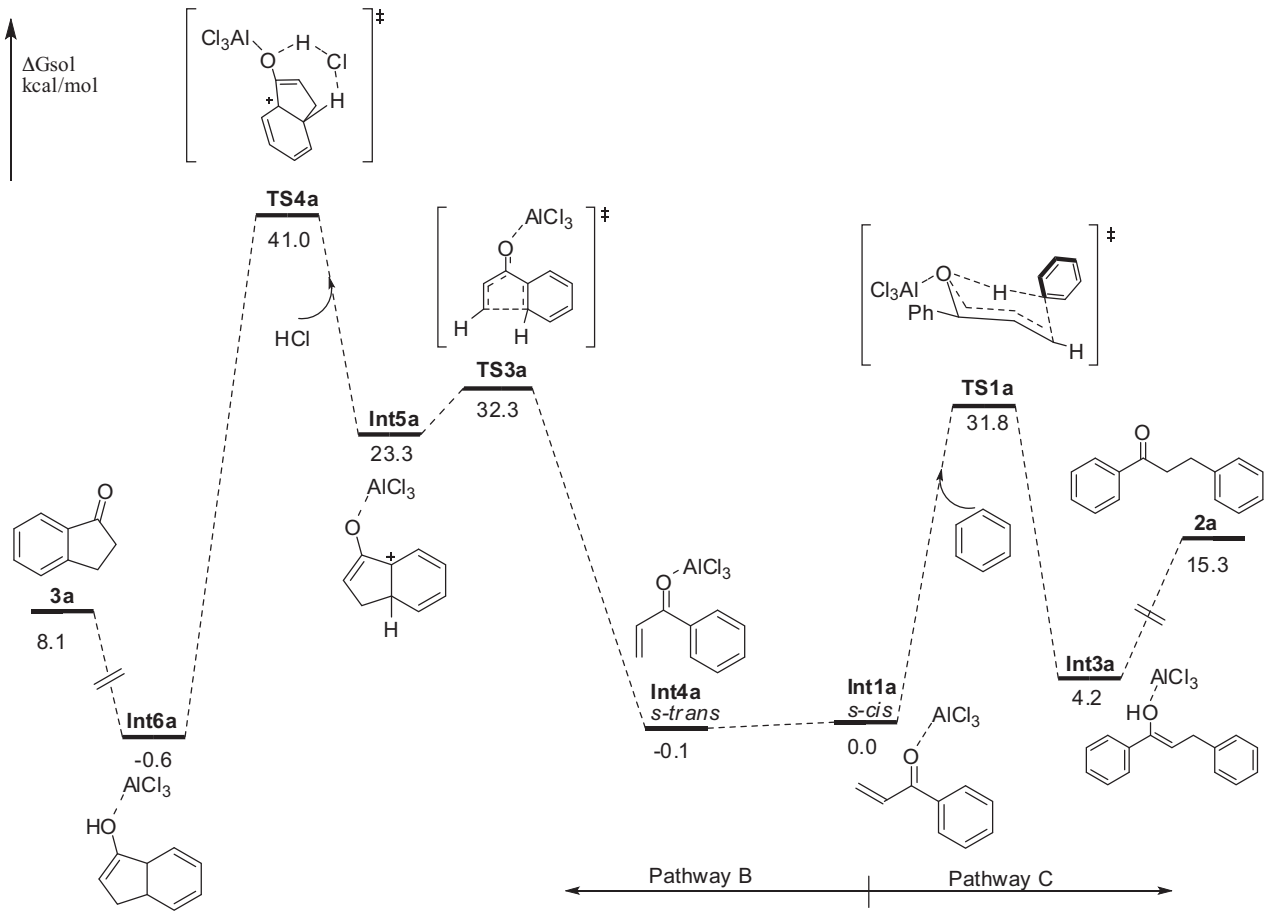


Fig. 1. DFT computed energy surface for the $AlCl_3$-promoted tandem Friedel–Crafts acylation and alkylation of 2-acryloyl chloride with benzene at M06-2X/(CPCM)/6-31G(d,p)//M06-2X/6-31G(d,p).

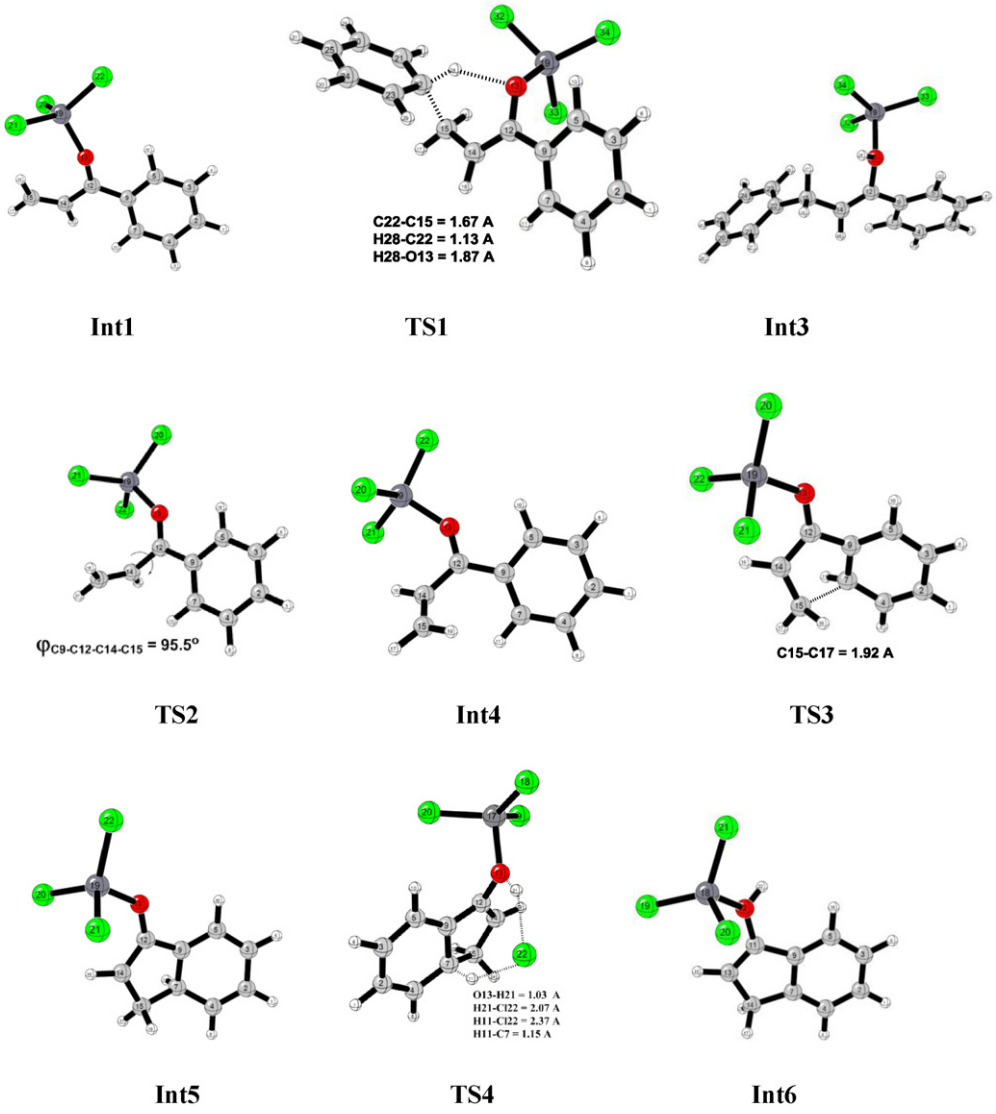


Fig. 2. Geometries (in Å) of transition state and intermediate structures in the $AlCl_3$-promoted tandem Friedel–Crafts acylation and alkylation of 2-acryloyl chloride with benzene, optimized at M06-2X/6-31G(d,p).

the reaction gave rise to a mixture of dihydrochalcone (**2a**) and 1-indanone (**3a**) under the catalysis of anhydrous aluminum chloride (Table 1, entries 5–7). 1-Indanone (**3a**) was obtained as major product if acryloyl chloride (**1a**) and benzene were mixed directly and stirred in the presence of aluminum chloride (Table 1, entry 5) due to high concentration of acryloyl chloride (**1a**) at the beginning of the reaction. However, dihydrochalcone (**2a**) became the major product (Table 1, entries 6 and 7), even almost sole product (Table 1, entries 8 and 9), when acryloyl chloride (**1a**) was diluted with benzene and the resulting solution was added dropwise into the reaction system both at room temperature and under refluxing. The results indicate that the dihydrochalcone (**2a**) was obtained in the highest yield of 81% when a solution of acryloyl chloride (**1a**) in benzene was added dropwise into a suspension of aluminum chloride (1.5 equiv.) in benzene during 3.3 h and then the resulting mixture was further stirred for 20 min under refluxing.

To extend the application of the $AlCl_3$-promoted tandem Friedel–Crafts acylation and alkylation, a series of 2-alkenoyl chlorides **1** were reacted with benzene under the optimized reaction conditions both at room temperature and under refluxing (Table 2). The results indicate that all 2-alkenoyl chlorides **1** produced dihydrochalcone derivatives **2** as major or sole products at room temperature (Table 2, entries 2, 5, 7, 9, 11, and 13). However, under refluxing condition, aliphatic 2-alkenoyl chlorides **1a–c**,**e** generally yielded 1-indanones **2a**, **b**, **e** as major products except for 3-methyl-2-butenoyl chloride (**1c**) (Table 2, entries 3 and 10), which generated dihydrochalcone **2c** and 1-indanone **3c** in similar yields (Table 2, entry 6), while both cinnamoyl chloride (**1d**) and 4-methylcinnamoyl chloride (**1f**) gave rise to dihydrochalcone (**2d**) as sole product as well (Table 2, entries 8 and 12). It is noted that cinnamoyl chloride (**1d**) and 4-methylcinnamoyl chloride (**1f**) produced the same dihydrochalcone (**2d**) as product at room temperature and under refluxing, revealing that the Friedel–Crafts alkylation is facile and reversible in the presence of aluminum chloride (Table 2, entries 12, and 13).

The results promote us to further investigate the generality of different arenes in the reaction. Three representative 2-alkenoyl chlorides **1a**, **c**, **f** were reacted with toluene at room temperature to afford the dihydrochalcones **2g–i** as chemoselective products in good yields possibly due to the high reactivity of toluene with an electron-donating methyl group on the benzene ring. For both acryloyl chloride (**1a**) and 2-methylacryloyl chloride (**1c**), a mixture of four different regiomeric dihydrochalcone derivatives **2a,c** were obtained because both *ortho* and *para* acylation

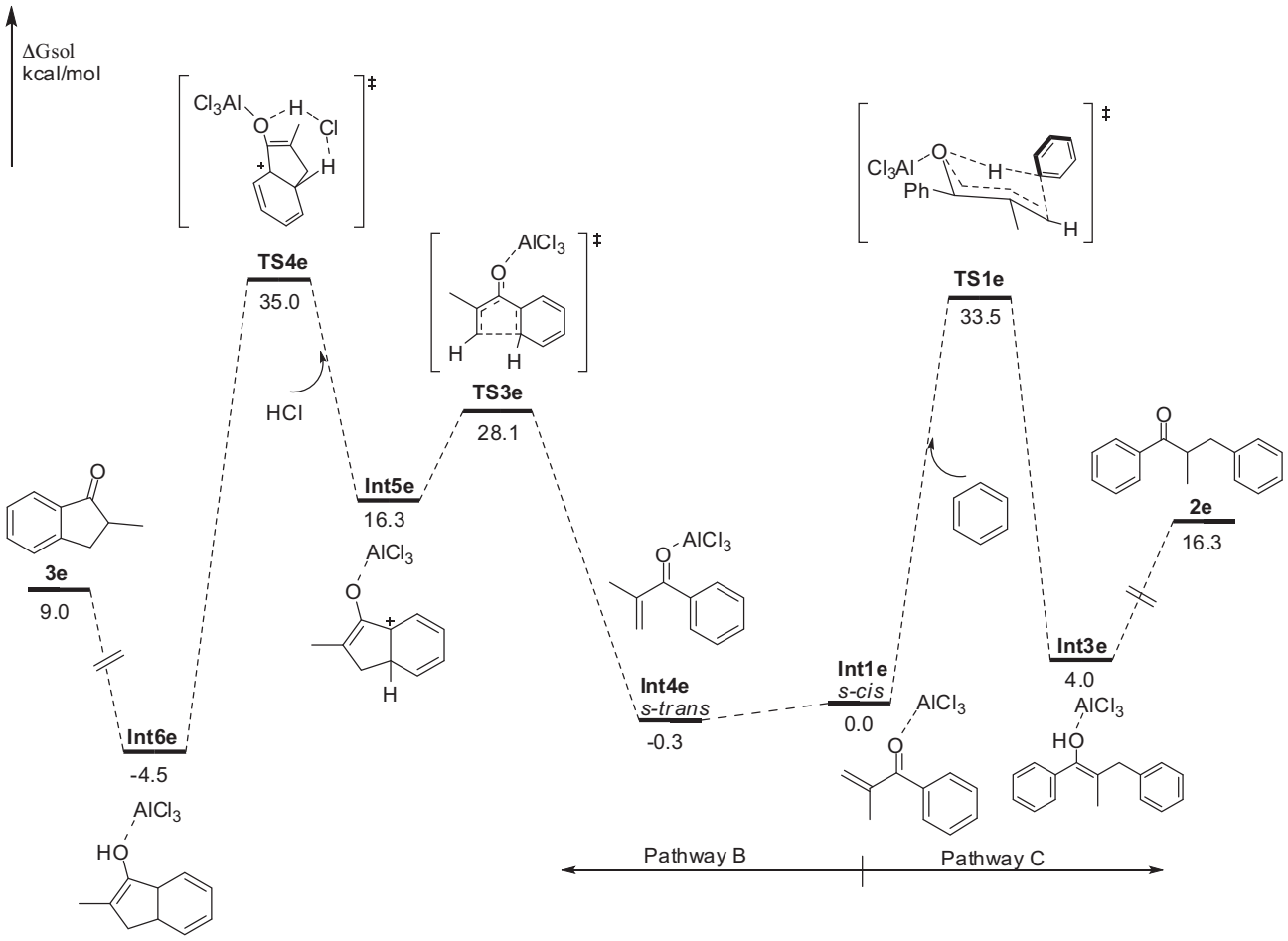


Fig. 3. DFT computed energy surface for the $AlCl_3$-promoted tandem Friedel–Crafts acylation and alkylation of methacryloyl chloride with benzene at M06-2X/(CPCM)/6-31G(d,p)//M06-2X/6-31G(d,p).

and alkylation occurred (Table 3, entries 1 and 2). However, 4-methylcinnamoyl chloride (**1f**) reacted with toluene to give rise to a mixture of 1,3,3-tri(4-methylphenyl)-1-propanone (**2ipp**) and 1-(2-methylphenyl)-3,3-di(4-methylphenyl)-1-propanone (**2iop**) in a ratio of 1.8:1.0, in which only *para*-alkylation occurred possibly due to steric hindrance in the 3-position of 4-methylcinnamoyl chloride (**1f**) (Table 3, entry 3). Treatment of **1a** with mesitylene (**4b**) also gave rise to the corresponding product **2j** in 90% yield exclusively. However, when **4b** was reacted with substituted 2-alkenoyl chlorides **1b**–**d**, only the Friedel–Crafts acylation took place, giving the acylation products **5b**–**d** in good yields. This is mainly attributed to the steric hindrance of the substituents between **4b** and **1b**–**d**, making the consequent alkylation difficult. Similarly, acylation product **5e** was also synthesized by the acylation of **1b** and *p*-xylene (**4c**) in 65% yield. We also attempted the reaction of acryloyl chloride (**1a**) and anisole with a strong electron-donating group in anisole as the solvent and hoped to prepare the corresponding dihydrochalcone in a good yield. Unfortunately, we failed because of the strong coordination between the oxygen atom in anisole and aluminum chloride. When aluminum chloride was added into anisole, solid complex generated from aluminum chloride and anisole, resulting in no desired reaction occurred.

While a precise reaction mechanism awaits further study, plausible competitive pathways are shown in Scheme 1. 2-Alkenoyl chlorides **1** and arenes initially undergo a Friedel–Crafts acylation in the presence of aluminum chloride to yield aluminum-coordinated 1-aryl-1-alkanone intermediates **Int1**, which further undergo a competitive process between an intermolecular Friedel–Crafts alkylation with another molecule of arenes involving the intermediacy of **Int2** and **Int3** to afford dihydrochalcones **2** through pathway A and an intramolecular of Friedel–Crafts alkylation (or the Nazarov cyclization) via the transition states **TS3** and **TS4** to yield 1-indanone **3** through pathway B in the reaction system. In general, the intramolecular reactions are more predominant than the intermolecular reactions, especially for the formation of five- and six-membered ring products. However, in the current reaction system, intermolecular products, dihydrochalcones **2**, were obtained as major or sole products in the most cases. This attracts our attention to deep understand the Friedel–Crafts alkylation mechanism. We presumed that the intermolecular Friedel–Crafts alkylation possibly undergoes a second pathway via a six-membered ring transition state in the alkylation reaction with relatively low energy barrier to facile the intermolecular alkylation (pathway C). To verify the proposed mechanism, we conducted the DFT calculation investigation into the intermolecular and intramolecular Friedel–Crafts alkylation at M06-2X level with the 6-31G(d,p) basis set. For intermolecular Friedel–Crafts alkylation, both acyclic and cyclic transition states were searched.

The reaction of acryloyl chloride (**1a**) and benzene was first selected as a model reaction for the calculational investigation. The energy surface was obtained and is shown in Fig. 1, in which the energy of the intermediate **Int1** was selected as the reference. For the intermolecular Friedel–Crafts alkylation, no transition state was located in the acyclic pathway (Pathway A), while the transition state was indeed located in the cyclic pathway with an activation energy of 31.8 kcal/mol (Pathway C). The

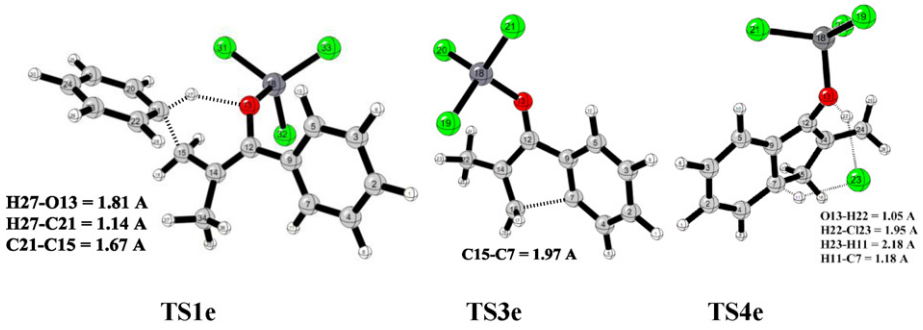


Fig. 4. Geometries (in Å) of transition state structures in the $AlCl_3$-promoted tandem Friedel–Crafts acylation and alkylation of methacryloyl chloride with benzene, optimized at M06-2X/6-31G(d,p).

intermediate **Int1a** undergoes a six-membered ring transition state **TS1a** to produce the aluminum chloride-coordinated enol intermediate **Int3a** with energy of 4.2 kcal/mol, which further generates the final product dihydrochalcone (**2a**) upon hydrolysis. In the transition structure **TS1a**, the forming C—C and O—H bond distances are 1.67 and 1.87 Å, respectively, and the breaking C—H bond distance is 1.13 Å, indicating that the alkylation occurs in a concerted but asynchronous cyclic fashion (Fig. 2). For the formation of 1-indanone (Pathway B), the intermediate **Int1a** needs first to rotate its single C—C bond to become *s*-trans isomer **Int4a** via a transition state with low energy. The intermediate **Int4a** cyclizes via a five-membered ring transition state **TS3a** with an activation free energy of 32.3 kcal/mol and the forming C—C bond distance of 1.92 Å to form an intermediate **Int5a** at energy of 23.3 kcal/mol, which further undergoes H-migration with the assistance of HCl molecule via a seven-membered ring transition state **TS4a**, requiring an activation free energy of 41.0 kcal/mol to generate an aluminum chloride-coordinated enol of 1-indanone **Int6a** at energy level of −0.6 kcal/mol. In the transition structure **TS4a**, the forming Cl—H and O—H bond distances are 2.37 and 1.03 Å, respectively, and the breaking Cl—H and C—H bond distances are 2.07 and 1.15 Å, respectively, indicating that the H-migration occurs in a cyclic fashion. The intermediate **Int6a** produces 1-indanone (**3a**) after hydrolysis. In the whole energy surface of the reaction, **TS4a** locates in the highest energy level, making the pathway B kinetically unfavorable in the formation of 1-indanone (**3a**). The computed results support the predominant formation of dihydrochalcone (**2a**) in the competitive alkylations in the reaction system.

The calculational investigation on the tandem reaction of different 2-alkenoyl chloride **1e** with benzene was conducted as well for comparison (Figs. 3 and 4). It is distinct from the reaction of **1a** that **1e** undergoes the Nazarov cyclization via the transition states **TS3e** and **TS4e** to yield 1-indanone **3e** with lower energy barrier relative to **TS3a** and **TS4a**. The decrease of the energy barrier on pathway B leads to this process feasible and makes it significantly competitive to pathway C, which is qualitatively consistent with the experimentally observed mixture of both products **2e** and **3e**.

5. Conclusion

In summary, tandem Friedel–Crafts acylation and alkylation of 2-alkenoyl chlorides with arenes in the presence of Lewis acids was investigated. Arenes and 2-alkenoyl chlorides underwent a tandem Friedel–Crafts acylation and alkylation to give rise to dihydrochalcone derivatives in good yields in the presence of anhydrous aluminum chloride. The scope, limitation, and mechanism of the reaction were studied and the mechanism was supported by the theoretical calculation. The intermolecular Friedel–Crafts alkylation for the formation of dihydrochalcones is more favorable than the intramolecular one for the generation of 1-indanones in the tandem reaction due to a stable six-membered ring transition state. The current reaction provides a convenient, environment-friendly, and practical route to the preparation of dihydrochalcone derivatives from arenes and 2-alkenoyl chlorides directly.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata.2012.09.005.

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