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Microwave-Assisted One-Pot Synthesis of 1-Indanones from Arenes and α,β-Unsaturated Acyl Chlorides

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A series of 1-indanones were synthesized in good yields via tandem Friedel−Crafts acylation and Nazarov cyclization of arenes and α,β-unsaturated acyl chlorides in the presence of aluminum chloride under microwave irradiation.

1-Indanones are important synthetic intermediates for pharmaceuticals and biologically active compounds[1] and ligands of olefin polymerization catalysts.[2] There are numerous methods available for the preparation of 1-indanones.[3] The intramolecular Friedel−Crafts acylation of 3-aryl carboxylic acids or the corresponding acyl chlorides catalyzed by Lewis acids and/or protic acids[4] has been one of the oldest and most widely used approaches because of its efficiency and convenience. The educts were prepared generally from arenes and α,β-unsaturated carboxylic acids. Actually, the intermolecular Friedel−Crafts reaction of arenes and α,β-unsaturated carboxylic acids has also been attempted to prepare 1-indanones.[1d,5,6] However, except for superacidic trifluoromethanesulfonic acid-induced cyclia-cyalkylation of arenes,[5] competitive Friedel−Crafts alkylation and/or acylation led to mixtures of 1-indanones, α,β-unsaturated aromatic ketones, and 3-aryl carboxylic acids, with the latter as major products in most cases.[7] Furthermore, Friedel−Crafts alkylation of 3-aryl α,β-unsaturated carboxylic acids affords 3,3-diaryl carboxylic acids, which will produce different structural isomers during the subsequent cyclization when the two aryl groups are different. Because the acyl chloride predominantly undergoes a Friedel−Crafts acylation rather than a Friedel−Crafts alkylation, to avoid competitive intermolecular Friedel−Crafts alkylation at the first step, active acyl chlorides should be more suitable reactants instead of the corresponding acids. However, although some 1-indanones could be prepared in good yields by the reaction of substituted benzenes and α,β-unsaturated acyl chloride under the catalysis of $AlCl_3$ or methanesulfonic acid, the substituted benzenes are limited to benzene and electron-rich substituted benzenes.[8]

Microwave irradiation has been widely applied in organic synthesis recently and achieved great success for many reactions,[9] including Friedel−Crafts acylations[10] and Nazarov cyclizations,[11] with high efficiency and yields. Herein, we present our results on the microwave-assisted one-pot synthesis of 1-indanones from substituted benzenes and α,β-unsaturated acyl chlorides in good yields.

First, we used identical conditions as reported by Koelsch et al. with crotonic acid and benzene as starting materials.[12] However, we failed to achieve the literature's yield (81.5%; a very low yield was obtained) in repeating the reaction several times. Instead, crotonic acid was recovered in all cases. To improve reactivity, we used more active crotonoyl chloride instead of crotonic acid and obtained a mixture of 3-methyl-1-

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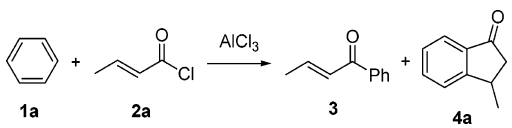
TABLE 1. Reaction of Benzene and Crotonoyl Chloride



1a 2a 3 4a

entry	solvent	reaction conditions	reaction time	yield of **3** (%)	yield of **4a** (%)
1	PhH	reflux	5 h	55	trace
2	CS_2	reflux	5 h	42	
3	$PhNO_2$	reflux	5 h		
4	$PhNO_2$	80 °C	5 h	3	11
5	$PhNO_2$	80 °C	16 h		12
6	$PhNO_2$	80 °C	18 h		10
7	$PhNO_2$	rt + 80 °C[a]	5 h + 18 h		22
8	$PhNO_2$	rt + 80 °C	24 h + 18 h		22
9	*o*-$C_6H_4Cl_2$	rt + 80 °C	5 h + 18 h		41
10	*o*-$C_6H_4Cl_2$	MW[b]	3 × 1.5 min		36
11	*o*-$C_6H_4Cl_2$	MW[b]	5 × 5 min		58
12	*o*-$C_6H_4Cl_2$	rt + MW[b]	5 h + 5 × 5 min		77
13	*o*-$C_6H_4Cl_2$	rt + MW[b]	5 h + 10 × 2 min		79

[a] Stirred at rt for 5 h and then at 80 °C for 18 h. [b] Irradiated under microwave at 185 °C at intervals. It takes about 30 s to achieve 185 °C under microwave conditions.

indanone, 1-phenyl-but-2-en-1-one, and 1,3-diphenyl-1-butanone (23% yield, not shown in Table 1) (entry 1, Table 1). To suppress the Friedel−Crafts alkylation of 1-phenyl-but-2-en-1-one and benzene, we decreased the amount of benzene to equimolar amount of acyl chloride. The one-pot reaction of crotonoyl chloride and benzene was selected as a model reaction to optimize the reaction conditions. The results are summarized in Table 1. 1-Phenyl-2-buten-1-one was obtained as a major product under refluxing in carbon disulfide as solvent. To improve the reaction temperature, nitrobenzene was used as solvent. Under refluxing conditions, the reaction mixture darkened, but no desired product was found. Lowering the reaction temperature to 80 °C provided the desired 3-methyl-1-indanone (**4a**), albeit in low yields. The yield of **4a** was improved when the solution of crotonoyl chloride and benzene in nitrobenzene was stirred at room temperature for 5 h and then heated at 80 °C for 18 h. A longer reaction time at room temperature of 24 h did not improve yields (entries 7 and 8, Table 1). Under the same conditions, but using *o*-dichlorobenzene as solvent, the yield of **4a** was remarkably increased (entry 9, Table 1). The yield was further improved when the reaction mixture was irradiated in a microwave field for 5 × 5 min (entry 11, Table 1). Finally, an optimized yield of 79% was achieved under microwave irradiation (10 × 2 min) at intervals. Pulsed microwave irradiation gave higher yields than irradiating the reaction mixture continuously for the same period of time. This phenomenon has also been discovered by other investigators, although the reason is not stated.[13] In our case, the continuous irradiation overheated the reaction mixture and caused black tarlike products. In recent years, an alternative method for performing microwave-assisted organic reactions, termed "enhanced microwave synthesis" (EMS), has been examined.[9b] In this method, microwave irradiation is administered while simultaneously externally cooling the reaction vessel with compressed air. It enables a greater amount of microwave energy to be introduced into a reaction while keeping the reaction temperature low.[14] This may offer an alternative operation to the pulsed approach.

After successful optimization, we expanded the scope of the reaction to various substituted benzenes (Table 2). Halobenzenes **1c**−**e** expectedly provided both structural isomers **4** and **5**. Most of them could be chromatographically separated and characterized via ^{1}H NMR. The 3,5-disubstituted isomers **4** were isolated as the major products, clearly indicating that the initial Friedel−Crafts acylation occurred predominantly para to the substituent. Biphenyl **1f** provided the 3,5-isomer **4f** exclusively. Toluene **1b** provided both isomers **4b** and **5b**. Interestingly, with the higher alkyl benzene homologues ethyl benzene (not shown), isopropyl benzene (**1g**), and *tert*-butyl benzene (**1h**), an increasing rate of concomitant dealkylation was observed. Consequently, ethyl benzene provided a mixture of the 5- and 7-isomers accompanied by **4a**. **1g** reacted to form a mixture of **4g** and **4a**, whereas **1h** suffered from complete dealkylation providing **4a** in 78% yield (entries 7 and 8, Table 2).

Second, **1a** and halobenzenes **1c**−**e** were reacted with cinnamoyl chloride **2b** under optimized conditions providing mixtures of the 5- and 7-isomers of the desired 1-indanones in yields of 72−97%.

When reacting the less-reactive halobenzenes with **2a** or **2b**, small amounts of dichloro-1-indanones were detected via mass spectroscopy, indicating that the solvent participated in the reaction. We evaluated the reactivity of the solvent by reacting *o*-dichlorobenzene with **2a** and provided actually only two of three possible isomers. 5,6-Dichloro-3-methyl-1-indanone (**4k**) and 4,5-dichloro-3-methyl-1-indanone (**4k′**) were obtained in yields of 20% and 29%, respectively, and were identified by their ^{1}H NMR spectra and NOE experiments (see Supporting Information). Both of them were formed from para acylation of *o*-dichlorobenzene and subsequent cyclization. Although *o*-dichlorobenzene can react with crotonoyl chloride and cinnamoyl chloride, it does not affect the desired reaction in most cases because of its lower reactivity.

The reaction process proceeds as follows: first, Friedel−Crafts acylation between a substituted benzene and an α,β-unsaturated acyl chloride occurs (stirring the reaction mixture at room temperature favors this process), and then an aromatic Nazarov cyclization gives rise to a 1-indanone. Although the cyclization of aryl vinyl ketones generally is considered a Nazarov cyclization[15] and it is generally considered that an aromatic ketone hardly undergoes a Friedel−Crafts alkylation, the Friedel−Crafts alkylation of 1-phenyl-but-2-en-1-one and benzene was observed (Table 1, entry 1). In the current case, the formed ketone **3** generally exists favorably in the s-cis conformation. Its $AlCl_3$-coordinated complex **6** should predominately convert to the s-trans conformation **7** because of the increasing size of the oxygen group. The carbon atom of the $AlCl_3$-coordinated carbonyl group could act as a carbocation as suggested in a recent report,[16] which could induce a C=C bond rearrangement to form an allylic or an allylic and benzylic carbocation **8**. The enolic carbocation **8** could easily undergo an intramolecular Friedel−Crafts alkylation to yield an indene-type intermediate **9**, which gives rise to the desired 1-indanone

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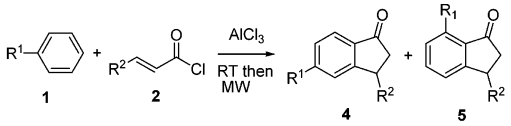
TABLE 2. Synthesis of 1-Indanones from Arenes and α,β-Unsaturated Acyl Chlorides[a]



1a: R^1 = H, **1b**: R^1 = Me, **1c**: R^1 = F, **1d**: R^1 = Cl, **1e**: R^1 = Br, **1f**: R^1 = Ph, **1g**: R^1 = *i*-Pr, **1h**: R^1 = *t*-Bu, **1i**: 1,3-xylene, **1j**: 1,4-xylene; **1k**: 1,2-dichlorobenzene; **2a**: R^2 = Me, **2b**: R^2 = Ph,

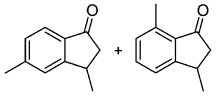
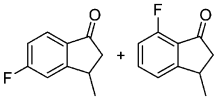
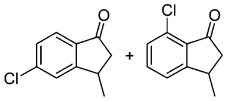
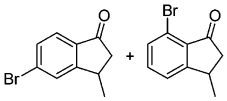
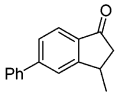
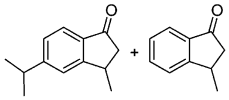
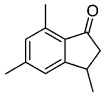
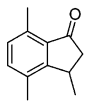
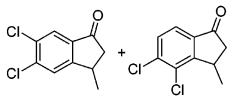
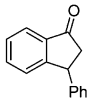
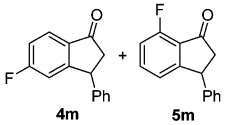
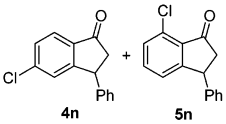
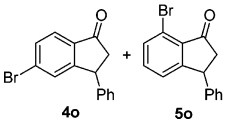
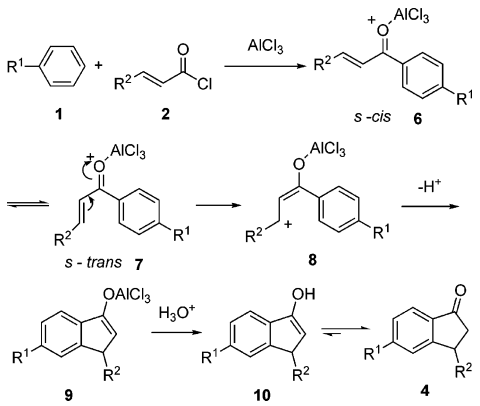
Entry	Starting materials	Product	Yield (%)[b] **4** + **5**	Product ratio **4** : **5**	Yield[c] (%) **4**	Yield[c] (%) **5**
1	**1a** + **2a**	 **4a**			79	
2	**1b** + **2a**	 **4b** **5b**		71:29[d]	70	29
3	**1c** + **2a**	 **4c** **5c**		65:35[d]	52	28
4	**1d** + **2a**	 **4d** **5d**		59:41[d]	50	34
5	**1e** + **2a**	 **4e** **5e**		64:36[d]	45	26
6	**1f** + **2a**	 **4f**			69	
7	**1g** + **2a**	 **4g** **4a**	50	78:22[e]		
8	**1h** + **2a**	 **4a**			78	
9	**1i** + **2a**	 **4i**			79	
10	**1j** + **2a**	 **4j**			65	
11	**1k** + **2a**	 **4k** **4k'**		41:59	20	29 (**4k'**)
12	**1a** + **2b**	 **4l**			72	

Table 2 (Continued)

Entry	Starting materials	Product	Yield (%)[b] **4 + 5**	Product ratio **4** : **5**	Yield[c] (%) **4**	Yield[c] (%) **5**
13	**1c + 2b**	 **4m** + **5m**	79	41:59[e]	30	
14	**1d + 2b**	 **4n** + **5n**	88	56:44[e]	45	
15	**1e + 2b**	 **4o** + **5o**		55:45[e]	53	44

[a] Stirred at rt for 5 h and then irradiated under microwave at 185 °C for 10 × 2 min at intervals. It takes about 30 s to achieve 185 °C under microwave conditions. [b] Total yield of the mixture of **4** and **5**. [c] Isolated yields after column chromatography. [d] Measured by ^{1}H NMR of the crude products. [e] Measured by HPLC analysis of the crude products on a ZORBAX Sil column (4.6 × 150 mm) with a mixture of hexane and 2-propanol (98:2, v/v) as eluent monitored at 254 nm.

SCHEME 1. Proposed Reaction Mechanism (Electrophilic Attack at Para Position Shown)



after hydrolysis and tautomerization (Scheme 1). It is impossible to distinguish whether the cyclization is an aromatic Nazarov cyclization or an intramolecular Friedel−Crafts alkylation. We considered it as a dual process.

In conclusion, a series of 1-indanones were synthesized in good yields via the tandem Friedel−Crafts acylation and Nazarov cyclization of substituted benzenes and α,β-unsaturated acyl chlorides in the presence of aluminum chloride under microwave irradiation. The current route is a practical and convenient method for the synthesis of 1-indanone derivatives from simple starting materials in a one-pot reaction, albeit it shows low regioselectivity for toluene and halobenzene.

Experimental Section

General Procedure for the Preparation of 1-Indanones. A dried round-bottom flask (50 mL) equipped with a condenser capped with an anhydrous $CaCl_2$ drying tube was charged with a solution of arene **1** (3 mmol), α,β-unsaturated acyl chloride (3.3 mmol), and anhydrous aluminum chloride (9 mmol) in 6 mL of dried *o*-dichlorobenzene. The solution was stirred at room temperature for 5 h and then irradiated under microwave at 185 °C for 10 × 2 min at intervals. It takes about 30 s to achieve 185 °C under microwave conditions. Between the two irradiations, the reaction temperature was allowed to cool to about 60 °C. After hydrolysis by addition of concentrated hydrochloric acid (15 mL) and ice, the resulting mixture was extracted with diethyl ether (3 × 25 mL). The combined organic phase was washed by 2 mol/L HCl (30 mL) twice, water, saturated sodium bicarbonate, and water and dried over anhydrous sodium sulfate. After removal of solvent, the residue was separated on a silica gel column with a mixture of petroleum ether (60−90 °C) and ethyl acetate (40:1 to 25:1, v/v) as eluent to afford the desired 1-indanone as product. To obtain pure product, most products were purified twice on the silica gel column.

5-Bromo-3-phenyl-1-indanone (4o). Colorless crystals. Mp 98−100 °C. R_f = 0.25 [ethyl acetate/ petroleum ether (60−90 °C) 1:15, v/v, silica gel plate]. IR (KBr) υ (cm^{-1}): 1713.4 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84−6.93 (m, 8H), 4.58 (dd, J = 8.2, 3.8 Hz, 1H), 3.23 (dd, J = 19.1, 8.2 Hz, 1H), 2.62 (dd, J = 19.1, 3.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 43.6, 46.4, 123.7, 126.7, 127.0, 128.3, 129.6, 130.9, 135.3, 136.7, 143.9, 156.5, 204.8. MS (EI) *m*/*z* (rel intensity, %): 286 (M^+, 84), 207 (M^+ − Br, 97), 77 (100). HRMS cacld for $C_{15}H_{11}BrO$ (M^+), 285.9993; found, 285.9985.

7-Bromo-3-phenyl-1-indanone (5o). Colorless crystals. Mp 68−70 °C. R_f = 0.38 [ethyl acetate/ petroleum ether (60−90 °C) 1:15, v/v, silica gel plate]. IR (KBr) υ (cm^{-1}): 1713.4 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83−7.11 (m, 8H), 4.58 (dd, J = 7.9, 3.7 Hz, 1H), 3.23 (dd, J = 19.3, 7.9 Hz, 1H), 2.69 (dd, J = 19.3, 3.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 44.4, 46.8, 123.4, 126.8, 126.9, 127.6, 127.8, 128.9, 135.0, 136.7, 143.6, 157.9, 205.9. MS (EI) *m*/*z* (rel intensity, %): 286 (M^+, 7), 208 (M^+ − PhH, 100), 207 (M^+ − Br, 27), 193 (12), 179 (38), 165 (27), 77 (18). HRMS cacld for $C_{15}H_{11}BrO$ (M^+), 285.9993; found, 285.9985.

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Supporting Information Available: The experimental details, the analytical data of products **4** and **5**, ^{1}H NMR and ^{13}C NMR spectra for the unknown 1-indanones **4g**, **4k**, **4k′**, **4m**, **4o**, **5c**−**e**, and **5o**, and the ^{1}H NMR NOE spectrum for the unknown 1-indanone **4k′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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