# Esters as Acylating Reagent in a Friedel−Crafts Reaction: Indium Tribromide Catalyzed Acylation of Arenes Using Dimethylchlorosilane

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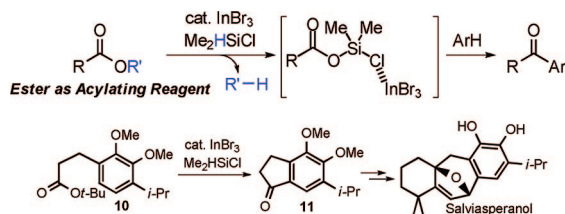
The Friedel−Crafts acylation of arenes with esters by dimethylchlorosilane and 10 mol % of indium tribromide has been achieved. The key intermediate $RCOOSi(Cl)Me_2$ is generated from alkoxy esters with the evolution of the corresponding alkanes. The scope of the alkoxy ester moiety was wide: *tert*-butyl, benzyl, allyl, and isopropyl esters were successful. In addition, we demonstrated the direct synthesis of the indanone intermediate **11** of salviasperanol from ester **10**.

Friedel−Crafts acylation is one of the fundamental methods for the synthesis of aromatic ketones, which is an important procedure in organic and industrial chemistry.[1] Conventionally, unstable and sensitive acylating reagents such as acid halides or acid anhydrides are employed with excess amounts of strong Lewis acids such as $AlCl_3$. Hence, acylation using a stable and easily accessed reagent under mild conditions is an important subject of organic synthesis. Many chemists have investigated the acylation of arenes with carboxylic acids. Most of these reaction systems, however, have encountered the limitations of very high temperatures[2] or excess amounts of fluorinated acid anhydrides.[3] Some cases were limited to an intramolecular reaction or activated arenes such as anisoles.[3e,4] Recently, we

also reported Friedel−Crafts acylation with carboxylic acids using $InCl_3$ and Me_2HSiCl,[5] which proceeded under mild conditions without the assistance of fluorinated acid anhydrides. However, this system requires a loading of at least 30 mol % of $InCl_3$ to obtain satisfactory results because of decomposition of $InCl_3$ by an acidic proton of carboxylic acids. In addition, only aromatic ethers such as anisole were applicable. For the solution of this problem, we focused on esters, which had no acidic proton and were more stable, less expensive, and easier to handle than conventional acylating reagents such as acid chlorides, acid anhydrides and carboxylic acids. Thus, esters can be an idealized acylating reagent. However, this ideal protocol remains a challenging problem because of the low reactivity of esters. To the best of our knowledge, there are a few practical reports of Friedel−Crafts acylation reactions with esters. One example can be found with Olah's report where excess CF_3SO_3H was used to generate an acyl cation from esters.[6,7] Fillion reported catalytic Friedel−Crafts acylation using Meldrum's acid derivatives.[8] However, in these systems there were some problems such as harsh conditions, a narrow range of substrates, and only intramolecular reaction. Herein we wish to report the Friedel−Crafts reaction system accommodating esters as acylation reagents, in which Me_2HSiCl and only 5−10 mol % of $InBr_3$ achieved the acylation of various arenes including benzene and toluene.

We optimized the reaction conditions by treating anisole with esters (Table 1). In all runs, ester, $InBr_3$, and silyl compounds were stirred at room temperature in 1,2-dichloroethane. After 2 h, anisole was added, and the resulting mixture was heated at 90 °C for 10 h. As expected, the use of ethyl benzoate resulted in no acylation (entry 1). Gratifyingly, the use of *tert*-butyl benzoate was found to give the desired ketone in a good yield (entry 2). The regioselective acylation took place at the *para* position of anisole and gave no other isomers. The use of either Me_3SiCl or Et_3SiH resulted in very poor yields (entries 3 and 4), and the combination of Me_3SiCl and Et_3SiH was also ineffective (entry 5). $InCl_3$ gave a lower yield than $InBr_3$ (entry 6), and other typical Lewis acids such as $BF_3 \cdot OEt_2$ and $AlCl_3$

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TABLE 1. Optimization of the Friedel−Crafts Acylation of Anisole from Benzoate[a]

entry	R	catalyst	additive	yield (%)[b]
1	Et	InBr$_3$	Me$_2$HSiCl	2
2	*t*-Bu	InBr$_3$	Me$_2$HSiCl	63
3	*t*-Bu	InBr$_3$	Me$_3$SiCl	16
4	*t*-Bu	InBr$_3$	Et$_3$SiH	0
5	*t*-Bu	InBr$_3$	Me$_3$SiCl + Et$_3$SiH	8
6	*t*-Bu	InCl$_3$	Me$_2$HSiCl	48
7	*t*-Bu	BF$_3$·OEt$_2$	Me$_2$HSiCl	0
8	*t*-Bu	AlCl$_3$	Me$_2$HSiCl	0

[a] Reaction conditions: ester (1.0 mmol), additive (1.2 mmol), ClCH$_2$CH$_2$Cl (2 mL), and anisole (1.5 mmol). [b] Yields were determined by ^{1}H NMR analysis.

SCHEME 1. Plausible Mechanism
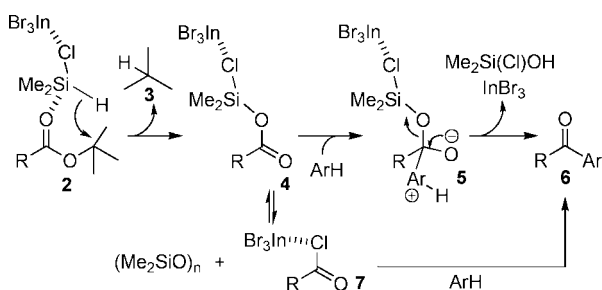
were not at all effective (entries 7 and 8). From these results, it is apparent that InBr$_3$ and Me$_2$HSiCl are indispensable for the acylation.

A plausible mechanism is shown in Scheme 1. The combined Lewis acid of InBr$_3$ and Me$_2$HSiCl selectively interacts with carbonyl oxygen,[9] in which the silicon atom acts as an acidic center.[10] The hydride transfer to a *tert*-butyl moiety occurs in the manner shown to generate RCO$_2$Si(Cl)Me$_2$ (**4**) with the evolution of isobutane (**3**),[11] while chloride transfer does not proceed because the nucleophilicity of the chloride moiety is decreased by the interaction with InBr$_3$. In fact, the generation of either PhCO$_2$Si(Cl)Me$_2$ or benzoyl chloride (PhCOCl) from *tert*-butyl benzoate and Me$_2$HSiCl in the presence of InBr$_3$ was confirmed by ^{13}C NMR,[12] and no generation of *tert*-butyl chloride was detected. There are two advantages of the *tert*-butyl group over the ethyl group in esters: (a) stabilization ability of the cationic charge and (b) steric protection of the ethereal oxygen from the Lewis acid.[13] The resulting RCO$_2$Si(Cl)Me$_2$ (**4**) is activated by InBr$_3$ through Me$_2$SiCl moiety to promote the direct acylation of arenes, and the desired ketone **6** is generated. An alternative reaction pathway involving the forma-

tion of acid chloride **7** cannot be excluded, as treatment of *tert*-butyl benzoate with Me$_2$HSiCl and InBr$_3$ at 90 °C in the absence of the arene nucleophile leads to formation of benzoyl chloride.[14]

The results of acylation reactions using various esters and arenes are summarized in Table 2. Acylations of *o*-haloanisoles regioselectively gave 5-substituted arenes (entries 1−3). Although furan species were not applicable as an arene, the reaction of thiophene proceeded smoothly without deactivation of the indium catalyst by the thiophene moiety (entry 4). It is notable that the acylation of toluene, xylene, and benzene also succeeded (entries 5−8), because no reaction took place when carboxylic acids were used instead of esters.[5] A variety of functionalized benzoates furnished the corresponding ketones in good to excellent yields. Both electron-rich and electron-deficient esters gave good yields (entries 9−11). The methyl ester moiety tolerated these conditions, and the acylation selectively proceeded with the *tert*-butyl ester moiety (entry 12). In contrast, using the CF$_3$SO$_3$H,[7] the acylation occurred with both the methyl and *tert*-butyl ester moieties to give the diketone.[15] *Ortho*-substituted esters and 2-naphthoic acid ester also reacted very well (entries 13−15). A simplified process was employed, in which the mixture of the *tert*-butyl ester, *p*-xylene, Me$_2$HSiCl, and InBr$_3$ was directly heated to give the desired ketones, although a small decrease in yield was observed (entries 16−18). Simple aliphatic esters afforded alkyl aryl ketones in moderate yields (entries 19 and 20). In these cases, 5 mol % of InBr$_3$ was more effective than 10 mol %. Chloro and acetyl groups tolerated the conditions (entries 21 and 22). A good result was also obtained in the reaction of the secondary alkyl ester (entry 23), and the intramolecular reaction also proceeded to afford the cyclic ketone (entry 24).

The scope of the alkoxy moiety in esters was assessed (Table 3). As expected from the stabilization ability of the cation, benzylic and allylic esters afforded high yields of more than 85% (entries 1−3). It was notable that even a secondary alkyl ester gave moderate yield of acylation product (entry 4). These results support the mechanism proposed in Scheme 1.

Friedel−Crafts alkylation often suffers from polyalkylation because of the higher reactivity of the alkylated products compared to that of the starting arenes.[1] To avoid this problem, conventionally a combination of Friedel−Crafts acylation and later Clemmensen and Wolf−Kishner reductions have generally been adopted. By contrast, our one-pot system promoted the acylation and successive reduction to selectively afford monoalkylation products by using excess amounts of Me$_2$SiHCl (Scheme 2). InBr$_3$ can act as a common catalyst in both steps.[9e]

An advantage of our acylating system was demonstrated by the direct synthesis of indanone intermediate **11** of salviasperanol from ester **10** (Scheme 3).[16] In contrast, Sarpong made **11** after the transformation of the ester to the acid chloride using two steps.

In summary, we have accomplished the employment of esters as acylation reagents in a catalytic Friedel−Crafts reaction of arenes, which is characteristically promoted by the combination of InBr$_3$ and Me$_2$HSiCl. Various arenes and esters were applicable, and functional moieties survived as a result of the mild reaction conditions.

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(11) Evolution of isobutane (14 mL) from 1 mmol of PhCOO^{t}Bu was confirmed and determined by ^{1}H NMR.

(12) ^{13}C NMR charts of either PhCO$_2$Si(Cl)Me$_2$ or PhCOCl are in Supporting Information. This intermediate was also reported in our previous paper.[5]

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(14) We confirmed the generation of acid chloride by ^{13}C NMR, and ^{13}C NMR charts are in Supporting Information.

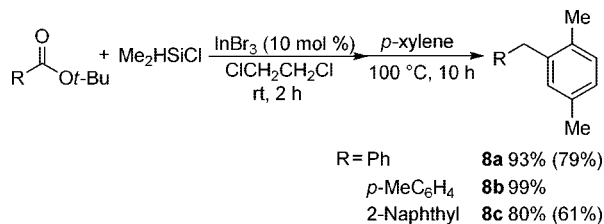(15) See Supporting Information.

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TABLE 2. Friedel−Crafts Acylation of Arenes with Esters[a]

entry	ester	Ar−H	conditions	product			yield (%)[c]
1	Ph–CO–Ot-Bu	o-X-anisole	A	Ph–CO–Ar(X, OMe)	X = F		**1b** 83 (72)
2			A		Cl		**1c** 84 (69)
3			A		Br		**1d** 86
4		thiophene	A	Ph–CO–thienyl			**1e** 70 (70)
5		X,Y-arene	B	Ph–CO–arene(X,Y)	X = H	Y = Me	**1f** 88[d,e]
6			B		o-Me	Me	**1g** 79 (72)
7			B		m-Me	Me	**1h** 87 (81)
8			C		H	H	**1i** 54
9	Ar–CO–Ot-Bu	p-xylene (Me)	B	Ar–CO–(Me)arene(Me)	Ar = p-MeOC₆H₄		**1j** 66[d]
10			B		p-MeC₆H₄		**1k** 96 (72)
11			B		p-ClC₆H₄		**1l** 89[d]
12			B		p-MeOCOC₆H₄		**1m** 57[d]
13			B		o-MeC₆H₄		**1n** 51 (43)
14			B		o-ClC₆H₄		**1o** 88
15			B		2-Naphthyl		**1p** 81 (56)
16			–[f]		Ph		**1q** 78
17			–[f]		p-MeC₆H₄		**1k** 63
18			–[f]		2-Naphthyl		**1p** 68
19	Alkyl–CO–Ot-Bu	anisole (OMe)	D	Alkyl–CO–(OMe)arene	Alkyl = n-C₁₀H₂₁		**1r** 52
20			D		PhCH₂(CH₂)₃		**1s** 64 (50)
21			D		ClCH₂(CH₂)₄		**1t** 64 (62)
22			D		AcOCH₂(CH₂)₄		**1u** 58
23			D		c-C₆H₁₁		**1v** 67 (59)
24	Ph(CH₂)₃CO–Ot-Bu		E	tetralone			**1w** 56

[a] Ester (1.0 mmol), Me₂HSiCl (1.2 mmol), and ClCH₂CH₂Cl (2 mL). [b] Conditions A: InBr₃ (10 mol %), ArH (1.5 mmol), 90 °C, 10 h. Conditions B: InBr₃ (10 mol %), ArH (1 mL), 100 °C, 10 h. Conditions C: InBr₃ (10 mol %), ArH (2 mL), 130 °C, 10 h, in a sealed tube. Conditions D: InBr₃ (5 mol %), ArH (1.5 mmol), 90 °C, 5 h. Conditions E: InBr₃ (30 mol %), 90 °C, 10 h. [c] Yields were determined by ¹H NMR analysis. Values in parentheses indicate isolated yield in different batch reactions in different scale (see Supporting Information). [d] InBr₃ (30 mol %). [e] (ortho:para) = (89:11). [f] Conditions: ester (1.0 mmol), Me₂HSiCl (1.2 mmol), ArH (1 mL), InBr₃ (10 mol %), and ClCH₂CH₂Cl (2 mL), 100 °C, 10 h. See the text.

SCHEME 2. Application to Monoalkylation of Alkylbenzenes[a]

R = Ph   **8a** 93% (79%)
p-MeC₆H₄   **8b** 99%
2-Naphthyl   **8c** 80% (61%)

[a] Ester (1.0 mmol), Me₂HSiCl (5.0 mmol), ClCH₂CH₂Cl (2 mL), and p-xylene (1 mL). Yields were determined by ¹H NMR analysis. Values in parentheses indicate isolated yield in different batch reactions in different scale (see Supporting Information).

Experimental Section

Typical Procedure of Step-by-Step Process (Condition A, Table 2, Entry 1). To a mixture of InBr₃ (0.1 mmol) and *tert*-butyl benzoate (1.0 mmol) in 1,2-dichloroethane (2 mL) was added dimethylchlorosilane (1.2 mmol) under nitrogen. The reaction mixture was stirred for 2 h at room temperature. Then, 2-fluoroanisole (1.5 mmol) was added, and the reaction mixture was heated for 10 h at 90 °C. The resulting mixture was poured into Et₂O (10 mL) and H₂O (10 mL). The solution was extracted with Et₂O, and the organic layer was dried over MgSO₄. The evaporation of the ether solution gave the crude product which was analyzed by NMR. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 85:15) to give the pure product. Mp: 67−68 °C. IR (KBr): 1643 (C=O) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): 7.75 (d, J = 7.2 Hz, 2H), 7.64−7.57 (m, 3H), 7.49 (t, J = 7.2 Hz, 2H), 7.02 (t, J = 7.2 Hz, 1H), 3.98 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): 194.5, 151.7, 151.6, 137.6, 132.2, 130.2, 129.7, 128.3, 127.7, 117.7, 112.1, 56.3. MS (EI, 70 eV): m/z 230 (M⁺, 55), 153 (M⁺ − C₆H₅, 100), 105 (M⁺ − C₆H₃FOMe, 29), 77 (C₆H₅, 23). HRMS (EI, 70 eV): calcd (C₁₄H₁₁FO₂) 230.0743 (M⁺), found 230.0741. Anal. Calcd for C₁₄H₁₁FO₂: C, 73.03; H, 4.82. Found: C, 72.99; H, 4.81.

TABLE 3. Scope of Alkoxy Moiety in Esters

entry	ester	yield (%)[a]
1	OR = \ O/\Ph	85
2	\O(CH)Ph	87 (78)
3	\O(CH)CH=CH2	63 (67)
4	\O(CH)(CH3)2	40

[a] Yields were determined by ^{1}H NMR analysis. Values in parentheses indicate isolated yield in different batch reactions in different scale.

SCHEME 3. Direct Synthesis of Indanone Intermediate 11 of Salviasperanol[a]
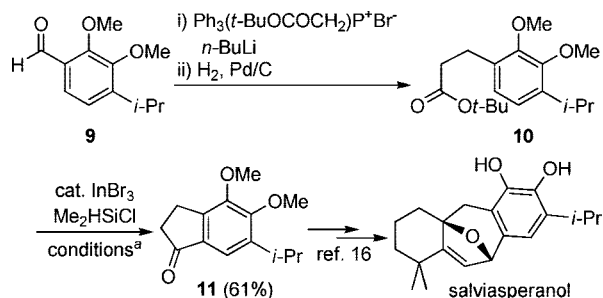
[a] Ester **10** (0.49 mmol), InBr$_3$ (40 mol %), Me$_2$HSiCl (0.56 mmol), and ClCH$_2$CH$_2$Cl (10 mL), rt, 2 h and 90 °C, 1 h. Isolated yield was 61%.

Typical Procedure for Simplified Process (Table 2, Entry 17). To a mixture of InBr$_3$ (0.1 mmol), *tert*-butyl 4-methylbenzoate (1.0 mmol), and *p*-xylene (1 mL) in 1,2-dichloroethane (2 mL) was added dimethylchlorosilane (1.2 mmol) under nitrogen. The reaction mixture was stirred for 10 h at 100 °C. The resulting mixture was poured into Et$_2$O (10 mL) and H$_2$O (10 mL). The solution was extracted with Et$_2$O, and the organic layer was dried over MgSO$_4$. The evaporation of the ether solution gave the crude product which

was analyzed by NMR. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 100:0) and distillation to give the pure product. Bp: 152 °C/0.4 mmHg. IR (neat): 1662 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): 7.70 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.19−7.16 (m, 2H), 7.10 (s, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): 198.6, 144.0, 138.9, 135.1, 134.7, 133.2, 130.71, 130.68, 130.2, 129.1, 128.6, 21.7, 20.8, 19.4. MS (EI, 70 eV): *m/z* 224 (M$^+$, 18), 223 (M$^+$ − 1, 23), 209 (M$^+$ − CH$_3$, 100). HRMS (EI, 70 eV): calcd (C$_{16}$H$_{16}$O) 224.1201 (M$^+$), found 224.1199. Anal. Calcd for C$_{16}$H$_{16}$O (224.30): C, 85.68; H, 7.19. Found: C, 85.40; H, 7.10.

Direct Synthesis of the Indanone Intermediate of Salviasperanol (Scheme 3). To a mixture of InBr$_3$ (0.2 mmol) and *tert*-butyl (4-isopropyl-2,3-dimethoxy)dihydrocinnamate **10** (0.49 mmol) in 1,2-dichloroethane (5 mL) was added Me$_2$HSiCl (0.56 mmol) at room temperature, and the reaction mixture was stirred for 2 h. Then, the reaction mixture was heated to 90 °C for 1 h. The resulting mixture was poured into Et$_2$O (10 mL) and H$_2$O (10 mL). The solution was extracted with Et$_2$O, and the organic layer was dried over MgSO$_4$. The evaporation of the ether solution gave the crude product. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 85:15) to give the product **11**. ^{1}H NMR (400 MHz, CDCl$_3$): 7.45 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.31 (sept, J = 7.6 Hz, 1H), 3.10−3.07 (m, 2H), 2.69−2.66 (m, 2H), 1.22 (d, J = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): 205.9, 155.8, 149.5, 146.2, 143.6, 133.3, 116.5, 60.8, 60.0, 36.3, 27.1, 23.3, 22.5. MS (EI, 70 eV): 234 (M$^+$, 52), 219 (M$^+$ − CH$_3$, 100). HRMS (EI, 70 eV): calcd (C$_{14}$H$_{18}$O$_3$) 234.1256 (M$^+$), found 234.1259.

Supporting Information Available: Reaction procedures, spectroscopic details of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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