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An efficient synthesis of diarylmethanes via $InCl_3{\cdot}4H_2O$-catalyzed dehydration of electron-rich arenes with trioxane

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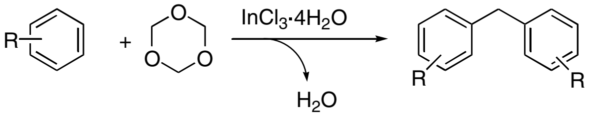
Abstract—A facile, efficient and environmentally benign procedure for the synthesis of diarylmethanes via the reaction of arenes with trioxane catalyzed by $InCl_3{\cdot}4H_2O$ was developed. The reactions of aromatic compounds bearing electron-donating group proceeded smoothly affording the corresponding diarylmethanes in good to excellent yields.

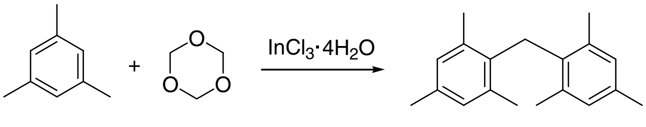
The development of catalytic organic synthesis using air-stable and water-tolerant inorganic salts as Lewis acid catalyst is one of the important and challenging subjects in organic synthesis chemistry. Recently, InX_3 (X = Cl, Br, I, OTf) has attracted considerable attention because of its diverse applications as a catalyst in organic synthesis.[1] Diarylmethane derivatives are useful intermediates in organic synthesis and polymer synthesis.[2] Diarylmethane moiety also exists in many organic compounds, which are physiologically active.[3] Diarylmethanes can be synthesized by the benzylation of arenes with benzyl chlorides or benzyl alcohols in the presence of various inorganic acid,[4] organic solid acid or other catalysts,[5] but both the substituted benzyl chlorides and benzyl alcohols are not easily available. The purpose of this work was to develop an efficient and simple method for synthesizing diarylmethanes directly from the easily available substituted arenes as starting materials, and we found that $InCl_3{\cdot}4H_2O$ displayed high catalytic activity to catalyze the dehydration of arenes with trioxane smoothly to afford diarylmethanes in good to excellent yield (Eq. 1).



(1)

We first performed the reaction of mesitylene with trioxane at 80, 100 and 120 °C to optimize the reaction conditions. As shown in Table 1, when a mixture of 6.0 mmol of mesitylene, 0.2 mmol of trioxane (0.6 mmol

Table 1. $InCl_3{\cdot}4H_2O$-catalyzed reaction of mesitylene with trioxane[a]



1a

Entry	Temp (°C)	Time (h)	Yield[b]
1	80	9	54
2	100	16	94
3	120	1	71
4	120	3	87
5	120	6	96 (87)

[a] The reactions were carried out using 0.2 mmol of trioxane, 6.0 mmol of mesitylene and 0.03 mmol of $InCl_3{\cdot}4H_2O$.

[b] GC yield based on 0.6 mmol amount of CH_2O moiety. Number in the parenthesis is the isolated yield.

Keywords: Arenes; Dehydration; Diarylmethanes; Indium(III) chloride tetrahydrate; Trioxane.

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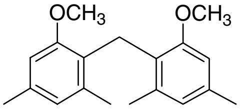
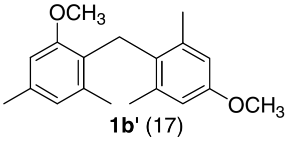
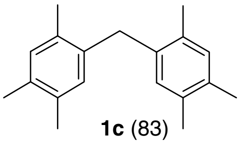
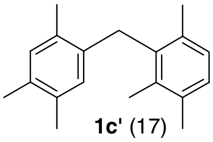
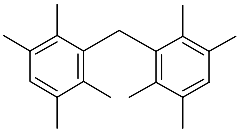
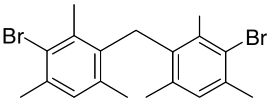
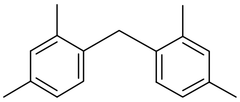
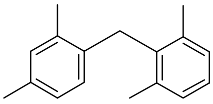
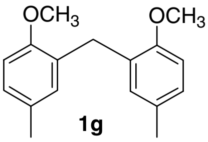
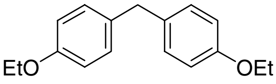
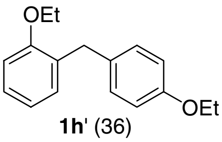
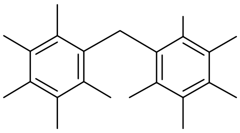
of CH_2O moiety) and 0.03 mmol of $InCl_3{\cdot}4H_2O$ was heated with stirring at 120 °C for 6 h, bis-(2,4,6-trimethyl-phenyl)methane **1a** could be obtained in the best yield of 96% (Table 1, entry 5). In order to suppress the further reaction of **1a** with trioxane, an excess amount of mesitylene was required. It was confirmed that the further reaction of **1a** with trioxane could be completely suppressed when the molar ratio of mesitylene and CH_2O was 10 or more. The reactions of a variety of arenes with trioxane under the identified reaction conditions in the presence of $InCl_3{\cdot}4H_2O$ were examined, and the results are summarized in Table 2.[6,7] According to the obtained results, the present dehydration reaction was greatly dependent on the orientation and reactivity effects of each group in benzene ring. For instance, good results were obtained in the cases of mesitylene and 3,5-dimethylanisole employed (Table 1, entry 5 and Table 2, entry 1),[8] but 1,2,4-trimethylbenzene showed somewhat low reactivity, the formation of two dehydrated products in a moderate yield (Table 2, entry 2), because the orientation effects of three methyl groups do not reinforce each other. Likewise, the reaction of 1,2,4,5-

Table 2. $InCl_3{\cdot}4H_2O$-catalyzed reaction of arene with trioxane[a]

Entry	Arene	Yield (%)[b]	Product (selectivity)[c]	
1	3,5-Dimethylanisole	>99 (93)	 **1b** (83)	 **1b'** (17)
2	1,2,4-Trimethylbenzene	75 (61)	 **1c** (83)	 **1c'** (17)
3	1,2,4,5-Tetramethylbenzene	52 (46)	 **1d**	
4	2-Bromomesitylene	46 (42)	 **1e**	
5	*m*-Xylene	67 (63)	 **1f** (89)	 **1f'** (11)
6	4-Methylanisole	95 (88)	 **1g**	
7[d]	Phenetole	83 (67)	 **1h** (58)	 **1h'** (36)
8	Pentamethylbenzene	69 (46)	 **1i**	

[a] The reactions were carried out using 0.2 mmol of trioxane, 6.0 mmol of arene and 0.03 mmol of $InCl_3{\cdot}4H_2O$.

[b] GC yield based on 0.6 mmol amount of CH_2O moiety, number in the parenthesis is the isolated yield.

[c] Ratio of isomers determined by GC.

[d] Three products.

tetramethylbenzene afforded the corresponding product in only 52% GC yield (Table 2, entry 3). In addition, because the introduction of a Br group deactivated the benzene ring, only 46% of product was obtained (Table 2, entry 4). In the two-substituted benzene ring, the reactivity was similarly dependent on the orientation of substituents. For example, *m*-xylene reacted with trioxane to give the dehydrated products in 67% GC yield (Table 2, entry 5), but in the case of *p*-xylene, only 11% of dehydrated product (determined by ^{1}H NMR of the crude reaction mixture) was formed. In the cases of 4-methylanisole and phenetole used, the high yields of the corresponding products were obtained, because the introduction of an OCH_3 or OEt group activated the benzene ring (Table 2, entries 6 and 7). The reaction of pentamethylbenzene with trioxane afforded 69% of dehydrated product (Table 2, entry 8).

However, 4-methoxybenzaldehyde, which bears an OCH_3 group (activating group) and a CHO group (deactivating group) reacted with trioxane to produce trace amount of desired product only. Furthermore, in the cases of chlorobenzene and nitrobenzene used, only small amount (<5%) of the dehydrated products were detected by GC. These results indicated that the present $InCl_3\cdot 4H_2O$-catalyzed dehydration reaction of arenes with trioxane showed good catalytic activity for electron-rich arenes only.

In summary, this letter provided an efficient and environmentally benign route to diarylmethanes via the dehydration of arenes with trioxane. The easy operation, ready availability and low cost of catalyst as well as good to excellent yield of diarylmethanes are the remarkable advantages of this procedure. Further application of $InCl_3\cdot 4H_2O$ as catalyst in organic synthesis is now in progress.

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6. A typical experiment for the synthesis of **1b** and **1b′** (Table 2, entry 1): A mixture of 3,5-dimethylanisole (816.0 mg, 6.0 mmol), 1,3,5-trioxane (18.0 mg, 0.2 mmol, 0.6 mmol of CH_2O) and $InCl_3\cdot 4H_2O$ (8.7 mg, 0.03 mmol) were stirred at 120 °C for 6 h. To this resulting reaction mixture, hexane (5.0 mL) as a diluent and octadecane (52.0 mg) as an internal standard for GC analysis were added. GC and GC–MS analyses of the mixture disclosed that bis-(4,6-dimethyl-2-methoxy-phenyl)methane **1b** and (4,6-dimethyl-2-methoxy-phenyl)-(2,6-dimethyl-4-methoxy-phenyl)methane **1b′** were formed in a ratio of 83:17. After removal of the insoluble materials, the filtrate was concentrated. Compound **1b** (136.0 mg, 0.48 mmol, in 80% yield) and **1b′** (22.0 mg, 0.08 mmol, in 13% yield) were isolated by preparative TLC (silica gel) using a mixture solvent of cyclohexane and diethyl ether (100:3) as an eluent. The total GC yield of **1b** and **1b′** was 99% confirmed by analysis of the reaction mixture.
7. Compounds **1b** and **1b′** are new compounds, **1a** and **1c**–**j** are known compounds, their structures have been confirmed by ^{1}H, ^{13}C NMR and GC–MS. The selected spectroscopic data are reported below.
   Bis-(2,4,6-trimethyl-phenyl)methane **1a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s × 4, 1H × 4), 4.00 (s, 2H), 2.24 (s × 2, 3H × 2), 2.10 (s × 4, 3H × 4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 135.0, 134.8, 129.4, 31.1, 20.9, 20.8; GC–MS *m*/*z* (% rel. inten.) 252 (M^+, 17), 237 (10), 207 (14), 193 (6), 178 (5), 165 (7), 132 (100), 117 (25), 91 (17).
   Bis-(4,6-dimethyl-2-methoxy-phenyl)methane **1b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (s × 2, 1H × 2), 6.50 (s × 2, 1H × 2), 3.98 (s, 2H), 3.70 (s × 2, 3H × 2), 2.26 (s × 2, 3H × 2), 2.11 (s × 2, 3H × 2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 138.4, 135.5, 125.5, 123.7, 109.4, 55.6, 22.9, 21.3, 19.7; GC–MS *m*/*z* (% rel. inten.) 284 (M^+, 43), 237 (11), 223 (6), 193 (6), 165 (10), 148 (100), 135 (40), 119 (31), 91 (23). Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.16; H, 8.51. (4,6-Dimethyl-2-methoxy-phenyl)-(2,6-dimethyl-4-methoxy-phenyl)methane. Compound **1b′**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54–6.53 (m, 4H), 3.97 (s, 2H), 3.76 (s, 3H), 3.68 (s, 3H), 2.29 (s, 3H), 2.18 (s, 6H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 156.9, 138.2, 137.9, 136.1, 130.9, 125.2, 124.0, 113.5, 109.8, 55.6, 55.1, 26.5, 21.3, 20.9, 20.0; GC–MS *m*/*z* (% rel. inten.) 284 (M^+, 34), 253 (3), 223 (3), 193 (3), 165 (7), 148 (100), 135 (28), 119 (12), 91 (18).
   Bis-(2,4,5-trimethyl-phenyl)methane **1c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (s × 2, 1H × 2), 6.67 (s × 2, 1H × 2), 3.79 (s, 2H), 2.23 (s × 2, 3H × 2), 2.21 (s × 2, 3H × 2), 2.16

(s × 2, 3H × 2); ^{13}C NMR (75 MHz, CDCl$_3$) δ 136.0, 134.0, 133.9, 132.8, 131.5, 130.5, 35.8, 19.3, 19.2, 19.1; GC–MS m/z (% rel. inten.) 252 (M$^+$, 61), 237 (77), 223 (14), 207 (22), 193 (11), 165 (10), 132 (100), 117 (25), 105 (10), 91 (21).

(2,4,5-Trimethyl-phenyl)-(2,5,6-trimethyl-phenyl)methane **1c′**: GC–MS m/z (% rel. inten.) 252 (M$^+$, 28), 237 (18), 223 (5), 207 (10), 191 (6), 165 (6), 132 (100), 105 (7), 91 (14).

Bis-(2,3,5,6-tetramethyl-phenyl)methane **1d**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.90 (s × 2, 1H × 2), 4.22 (s, 2H), 2.25 (s × 4, 3H × 4), 2.05 (s × 4, 3H × 4); ^{13}C NMR (75 MHz, CDCl$_3$) δ 139.0, 133.7, 132.8, 129.5, 33.4, 20.9, 16.3; GC–MS m/z (% rel. inten.) 280 (M$^+$, 46), 265 (23), 235 (10), 220 (9), 178 (5), 165 (6), 146 (100), 115 (15), 91 (24), 77(8).

Bis-(3-bromo-2,4,6-trimethyl-phenyl)methane **1e**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.87 (s × 2, 1H × 2), 4.11 (s, 2H), 2.35 (s × 2, 3H × 2), 2.21 (s × 2, 3H × 2), 2.07 (s × 2, 3H × 2); ^{13}C NMR (75 MHz, CDCl$_3$) δ 136.9, 136.4, 135.8, 135.3, 130.7, 126.6, 33.8, 21.1, 20.9; GC–MS m/z (% rel. inten.) 410 (M$^+$, 20), 395 (2), 329 (5), 299 (5), 235 (48), 212 (100), 189 (6), 115 (27), 91 (25).

Bis-(2,4-dimethyl-phenyl)methane **1f**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.06 (s × 2, 1H × 2), 6.97–6.81 (m, 4H), 3.88 (s, 2H), 2.35 (s × 2, 3H × 2), 2.28 (s × 2, 3H × 2); ^{13}C NMR (75 MHz, CDCl$_3$) δ 136.4, 135.6, 131.0, 129.1, 126.7, 36.0, 21.0, 19.6; GC–MS m/z (% rel. inten.) 224 (M$^+$, 62), 209 (87), 194 (30), 179 (36), 165 (19), 152 (8), 128 (7), 118 (100), 91 (26), 77 (20). (2,4-Dimethyl-phenyl)-(2,6-dimethyl-phenyl)methane **1f′**: GC–MS m/z (% rel. inten.) 224 (M$^+$, 24), 209 (20), 194 (11), 179 (13), 165 (9), 118 (100), 135 (28), 91 (18).

Bis-(2-methoxy-5-methyl-phenyl)methane **1g**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.97–6.76 (m, 6H), 3.91 (s, 2H), 3.80 (s × 2, 3H × 2), 2.23 (s × 2, 3H × 2); ^{13}C NMR (75 MHz, CDCl$_3$) δ 155.6, 131.3, 129.5, 129.1, 127.3, 110.4, 55.6, 29.5, 20.6; GC–MS m/z (% rel. inten.) 256 (M$^+$, 100), 241 (8), 225 (20), 209 (30), 178 (12), 165 (33), 135 (38), 121 (97), 105 (61), 91 (22), 65 (9).

Bis-(4-ethoxy-phenyl)methane **1h**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.10 (d × 2, 2H × 2, $J = 8.8$ Hz), 6.83 (d × 2, 2H × 2, $J = 8.8$ Hz), 4.02 (q × 2, 2H × 2, $J = 7.2$ Hz), 3.93 (s, 2H), 3.88 (s, 4H), 1.42 (t × 2, 3H × 2, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.3, 133.7, 129.8, 114.9, 63.5, 40.2, 15.0; GC–MS m/z (% rel. inten.) 256 (M$^+$, 100), 227 (64), 211 (59), 199 (60), 183 (40), 169 (12), 152 (42), 141 (17), 128 (22), 115 (27), 107 (59), 77 (21). (2-Ethoxy-phenyl)-(4-ethoxy-phenyl) methane **1h′**: GC–MS m/z (% rel. inten.) 256 (M$^+$, 70), 227 (100), 199 (66), 181 (27), 152 (36), 128 (13), 107 (21), 77 (14). Another isomer: GC–MS m/z (% rel. inten.) 256 (M$^+$, 53), 227 (13), 181 (35), 165 (12), 152 (33), 121 (100), 107 (32), 77 (14).

Bis-(2,3,4,5,6-pentamethyl-phenyl)methane **1i**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.20 (s, 2H), 2.26 (s × 2, 3H × 2), 2.21 (s × 4, 3H × 4), 2.07 (s × 4, 3H × 4); ^{13}C NMR (75 MHz, CDCl$_3$) δ 136.7, 132.4, 132.2, 33.8, 17.2, 17.0; GC–MS m/z (% rel. inten.) 308 (M$^+$, 20), 293 (12), 160 (100), 145 (18), 136 (17), 105 (11), 91 (13).

8. On the basis of ^{1}H, ^{13}C NMR as well as the orientation and reactivity effects of substituting groups in the benzene ring, the major products **1b**, **1c**, **1f** and **1i** were assigned to the structures shown in Table 2.