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An efficient synthesis of unsymmetrical diarylmethanes from the dehydration of arenes with benzyl alcohols using $InCl_3 \cdot 4H_2O$/acetylacetone catalyst system

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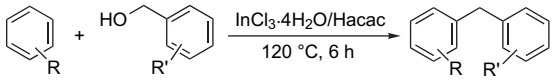
Abstract—An efficient and practical synthesis of unsymmetrical diarylmethanes has been achieved from the dehydration of arenes with benzyl alcohols in the presence of catalytic amount of $InCl_3 \cdot 4H_2O$/acetylacetone.

1. Introduction

Benzylation of arenes is an important reaction in the synthesis of diarylmethane derivatives, which are important and useful intermediates in organic and polymer synthesis.[1] Furthermore, some of diarylmethane derivatives have interesting biological and physiological properties.[2] The common synthetic method for diphenylmethane derivatives has been the Friedel–Crafts type alkylation of arenes with benzyl halides historically. But the use of benzyl halides as benzylating agent is undesirable from an environmental point of view, since this procedure not only requires to use the acid catalysts, which are corrosive (e.g., H_2SO_4, $AlCl_3$, BF_3, etc.), but also generates a large amount of waste materials during isolation of the products.[3] Therefore, recently the benzylation of arenes with benzyl alcohols as benzylating reagent under various catalytic conditions has been investigated extensively[4] and become an attractive method for the synthesis of diarylmethane derivatives, because (1) it generates only H_2O as byproduct; (2) benzyl alcohols are more readily available than the corresponding halides in most cases.

On the other hand, developing the catalytic organic reactions using air-stable and water-tolerant inorganic salts as Lewis acid catalysts is one of the promising and challenging subjects in modern synthetic chemistry. Recently, InX_3 (X=Cl, Br, I, OTf) have been attracting considerable attention because of its broad applications as catalysts in organic synthesis.[5] In particular, InX_3 have been the efficient catalysts for the carbon–carbon bond formation.[6] In our previous work, we have demonstrated that $InCl_3 \cdot 4H_2O$ is an efficient catalyst for the dehydration of electron-rich arenes with trioxane affording symmetrical diarylmethane derivatives.[7] As a continuation of our research, here we wish to report the results of $InCl_3 \cdot 4H_2O$/acetylacetone-catalyzed benzylation of arenes with a variety of benzyl alcohols to produce unsymmetrical diarylmethane derivatives in good to excellent yields (Eq. 1).



(1)

2. Results and discussion

We initiated our studies to examine the dehydration reaction of mesitylene (**1a**) with a variety of benzyl alcohols and the results are listed in Table 1. When a mixture of 20.0 mmol of **1a**, 2.0 mmol of benzyl alcohol (**2a**), and 0.1 mmol of $InCl_3 \cdot 4H_2O$ was heated with stirring at 120 °C for 24 h, GC and GC–MS analyzes of the reaction mixture indicated that phenyl-(2,4,6-trimethylphenyl)methane (**3a**) was formed in 32% GC yield (entry 1).[8] The yield of **3a** was drastically affected by the reaction temperature, if the reaction was carried out at 150 °C for 24 h, **3a** could be obtained in 86% isolated yield (92% of GC yield, entry 2). In order to develop an efficient and practical catalytic system for the present benzylation reaction, we have checked the reaction by addition of some additives, and found that the addition of catalytic amount of acetylacetone (Hacac) could accelerate the dehydration reaction significantly. Thus, repeating the reaction by addition of Hacac (15 mol %) at 120 °C for 6 h resulted in the formation of **3a** in 93% of GC yield (entry 3). These encouraging results led us to examine the benzylation

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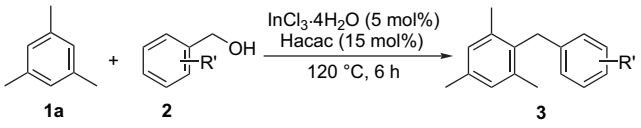
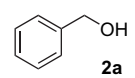
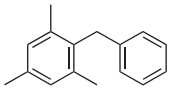
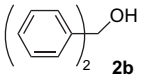
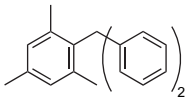
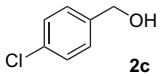
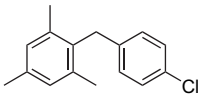
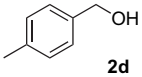
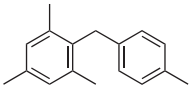
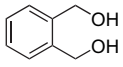
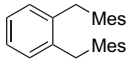
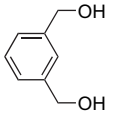
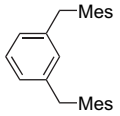
Table 1. $InCl_3 \cdot 4H_2O$-catalyzed dehydration of mesitylene with benzyl alcohols[a]



1a **2** **3**

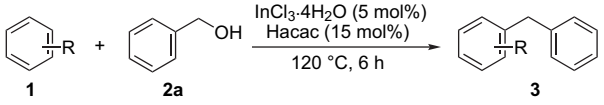
Entry	Benzyl alcohol	Product **3**	Yield[b] (%)
1[c]	 **2a**	 **3a**	(32)
2[d]	**2a**	**3a**	86 (92)
3	**2a**	**3a**	86 (93)
4	 **2b**	 **3b**	82
5	 **2c**	 **3c**	87
6	 **2d**	 **3d**	87
7	 **2e**	 **3e**	67
8	 **2f**	 **3f**	39

[a] Reactions were carried out at 120 °C for 6 h using 20 mmol of **1a**, 2 mmol of **2**, 0.1 mmol of catalyst, and 0.3 mmol of Hacac.
[b] Isolated yield based on the amount of **2** used. Numbers in parentheses are GC yields.
[c] Without Hacac, at 120 °C for 24 h.
[d] Without Hacac, at 150 °C for 24 h.

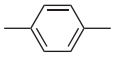
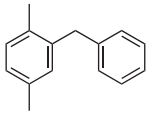
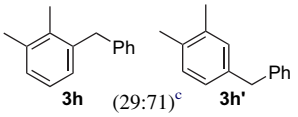
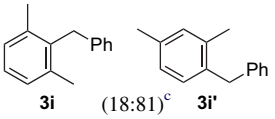
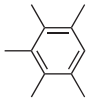
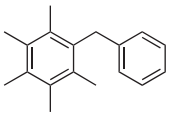
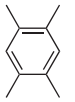
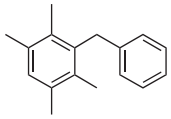
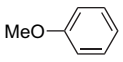
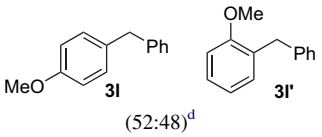
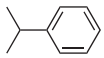
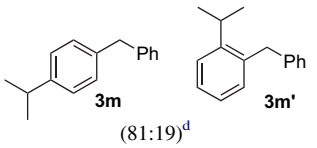
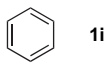
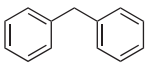
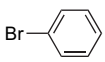
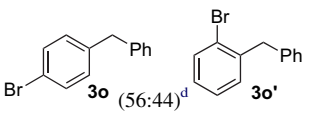
of **1a** with a variety of benzyl alcohols in the presence of $InCl_3 \cdot 4H_2O$/Hacac. As shown in Table 1, diphenylmethanol, *para*-chloro, *para*-methyl-substituted benzyl alcohols underwent the benzylation smoothly to give the corresponding dehydrated products in high isolated yields (entries 4–6). In addition, under the same reaction conditions, the reaction of **1a** with 1,2- or 1,3-benzenedimethanol afforded the expected products **3e** and **3f** in fair to good isolated yields (entries 7 and 8).

The results of the $InCl_3 \cdot 4H_2O$/Hacac-catalyzed benzylation of several arenes with **2a** are summarized in Table 2. The di-, penta- and tetramethyl substituted arenes showed high reactivity to produce the corresponding benzylated products in high yields (entries 1–5). In the cases of *o*-xylene (**1c**) and *m*-xylene (**1d**), the reactions gave a mixture of two benzylated products, which were not separable. In the benzylation of anisole (**1g**) and cumene (**1h**), the benzylated products were obtained in 81 and 77% isolated yields, respectively (entries 6 and 7). In both cases, two regioisomers were

Table 2. $InCl_3 \cdot 4H_2O$-catalyzed dehydration of arene with benzyl alcohol[a]



1 **2a** **3**

Entry	Arene	Product **3**	Yield[b] (%)
1	 **1b**	 **3g**	92
2	 **1c**	 **3h** (29:71)[c] **3h'**	90
3	 **1d**	 **3i** (18:81)[c] **3i'**	62
4	 **1e**	 **3j**	87
5	 **1f**	 **3k**	93
6	 **1g**	 **3l** **3l'** (52:48)[d]	81
7	 **1h**	 **3m** **3m'** (81:19)[d]	77
8	 **1i**	 **3n**	75
9	 **1j**	 **3o** (56:44)[d] **3o'**	41

[a] Reactions were carried out at 120 °C for 6 h using 20 mmol of **1**, 2 mmol of **2a**, 0.1 mmol of catalyst, and 0.2 mmol of Hacac.
[b] Isolated yield based on the amount of **2** used.
[c] Determined by ^1H NMR.
[d] Determined by GC.

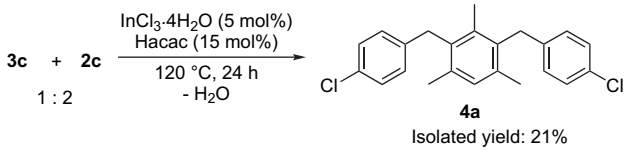
formed, only regioisomers **3l** and **3l′** could be further separated by careful preparative TLC (silica gel) isolation.

$InCl_3 \cdot 4H_2O$/Hacac catalyst system could also be applied to the reactions of neutral and electron-deficient arenes,

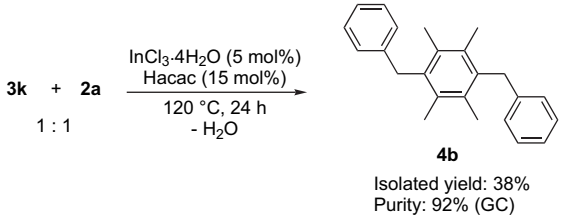
although the desired benzylated products were obtained in somewhat low yields. In the case of benzene (**1i**), the monobenzylated product **3n** was isolated in 75% yield (entry 8). The reaction of bromobenzene (**1j**) with **2a** afforded an isomeric mixture in moderate yield (entry 9). In this case, unfortunately, the separation of two isomers was not successful either.

Attempts to develop the multi-benzylation of arene in one-pot by using the excess amount of benzyl alcohols (5.0 equiv) were not successful, since the use of the excess amount of benzyl alcohols not only resulted in the great decrease of catalytic activity of catalyst system for the formation of **3**, but also produced a complicated mixture of the benzylated products.[8] In addition, in these cases the formation of dibenzyl ether became the main reaction.

We have also examined briefly the reactions of **3c** and **3k** with the electron-deficient benzyl alcohol (**2c**) (**3c/2c**=1:2; **3k/2c**=1:1), the desired dibenzylated products **4a** and **4b** were obtained in low yields after a prolonged reaction time (Schemes 1 and 2). Compounds **3c** and **3k** could be recovered in 76 and 53%, respectively. In both cases, the formation of bis(4-chlorobenzyl)ether was also observed. Furthermore, when **3k** was employed, there were three more isomers with the same molecular weight (MS) as **4b**, indicating that the benzylation also took place in the aromatic ring of benzyl group in **3k**. It resulted in the difficult isolation of **4b**.



Scheme 1.



Scheme 2.

It is clear that $InCl_3 \cdot 4H_2O$ as a Lewis acid catalyzes the benzylation of arenes with benzyl alcohols, and the addition of Hacac can greatly increase its catalytic activity. In order to get insight into the role of Hacac, we assumed that $In(acac)_3$ might be formed in situ. Therefore, we prepared and examined the catalytic activity of $In(acac)_3$.[9] But unfortunately, $In(acac)_3$ could not catalyze the present dehydration at all under the similar reaction conditions, both starting materials were completely recovered. Attempts to prepare $InCl(acac)_2$ or $InCl_2(acac)$ failed, since we usually got a mixture of indium complexes. Therefore, the catalytic species (or its precursor) is not clear at the present stage.

3. Conclusion

In summary, we have developed an efficient and practical catalyst system of $InCl_3 \cdot 4H_2O$/Hacac for the dehydration of arenes with benzyl alcohols to afford unsymmetrical diarylmethane derivatives in good to high yields. The present catalytic procedure provides a valuable alternative for benzylation of arenes with benzyl alcohols. Further study to apply $InCl_3 \cdot 4H_2O$/Hacac as catalyst to another carbon–carbon bond formation is now in progress.

4. Experimental section

4.1. General method

All organic starting materials are analytically pure and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Joel JNM-ECA300 spectrometer at 300 and 75 MHz, respectively. ^1H chemical shifts (δ) were referenced to TMS, and ^{13}C NMR chemical shifts (δ) were referenced to internal solvent resonance. GC analyzes of organic compounds were performed on an Agilent Technologies 1790 GC (with a TC-WAX capillary 25 m column) instrument. Mass spectra were obtained on a Hewlett 5890 Packard SERIES II GC/MS spectrometer with a PEG-25M column. High-resolution mass spectra were obtained with a ZAB-HS mass spectrometer in the Department of Chemistry of Peking University. Element analyzes were obtained with a Flash EA 1112 element analyzer in the Institute of Chemistry, Chinese Academy of Sciences.

4.2. A typical procedure for the benzylation of mesitylene (1a) with benzyl alcohol (2a): formation of 3a (Table 1, entry 3)

A mixture of mesitylene (**1a**) (2.4 g, 20.0 mmol), benzyl alcohol (**2a**) (216.0 mg, 2.0 mmol), $InCl_3 \cdot 4H_2O$ (29.5 mg, 0.1 mmol), and Hacac (ca. 30 μL, 0.3 mmol) was stirred at 120 °C for 6 h. To this resulting reaction mixture, hexane (15.0 mL) as diluent and *n*-docosane (124.7 mg) as an internal standard for GC analysis were added. After GC and GC–MS analyzes, the insoluble materials were removed by filtration. The solvent was then removed by rotary evaporation and mesitylene was then distilled out under reduced pressure (ca. 100 Torr). The resulting residue was dissolved in toluene (ca. 2 mL) and subjected to column chromatographic purification (silica gel, eluted with hexane, then a mixture of hexane and CH_2Cl_2 (20:1)) to afford **3a** as a colorless oil (362.0 mg, 1.72 mmol, 86%). The GC yield of **3a** in the reaction mixture was 93%.

The selected spectroscopic data for the new compounds **3c**, **3f**, and **4a** are shown below. The characterization data for known products and the copies of ^1H and ^{13}C NMR for all the products are provided in Supplementary data.

4.3. Characterization data of 3c, 3f, and 4a

4.3.1. (4-Chlorophenyl)-(2,4,6-trimethylphenyl)methane 3c. Viscous colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, 2H, J=8.2 Hz), 6.92 (d, 2H, J=8.2 Hz), 6.88 (s,

2H), 3.96 (s, 2H), 2.28 (s, 3H), 2.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 136.9, 135.9, 133.2, 131.4, 129.2, 129.0, 128.4, 34.1, 20.9, 20.1 GC–MS *m*/*z* (% rel inten.) 244 (M^+, 77), 229 (100), 194 (42), 179 (46), 132 (55), 91 (35); Anal. Calcd for $C_{16}H_{17}Cl$: C, 78.51; H, 7.00. Found: C, 78.18; H, 6.99.

4.3.2. 1,3-Bis[(2,4,6-trimethylphenyl)methyl]benzene 3f. Needle crystal (from ethanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (m, 1H), 6.85 (s, 4H), 6.74–6.72 (m, 3H), 3.93 (s, 4H), 2.28 (s, 6H), 2.16 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 136.9, 135.5, 133.9, 128.8, 128.3, 127.9, 125.0, 34.6, 20.9, 20.1; GC–MS *m*/*z* (% rel inten.) 342 (M^+, 67), 327 (15), 222 (41), 207 (100), 192 (30), 133 (76), 91 (31); Anal. Calcd for $C_{26}H_{30}$: C, 91.17; H, 8.83. Found: C, 90.86; H, 9.01. HRMS calcd for $C_{26}H_{30}$: 342.2348, found: 342.2349.

4.3.3. 2,6-Bis(4-chlorobenzyl)-1,3,5-trimethylbenzene 4a. Needle crystal (from a mixture of cyclohexane and dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, 4H, J=8.3 Hz), 6.96 (s, 1H), 6.92 (d, 4H, J=8.3 Hz), 4.01 (s, 4H), 2.22 (s, 6H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 136.1, 135.3, 134.4, 131.4, 130.2, 129.1, 128.5, 34.8, 20.2, 16.1; GC–MS *m*/*z* (% rel inten.): 368 (M^+, 100), 256 (82), 192 (33), 165 (9), 152 (4), 139 (4), 125 (35), 115 (6), 91 (5), 77 (4).

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Supplementary data

Characterization data for the known products and copies of ^{1}H and ^{13}C NMR charts of **3** and **4**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.093.

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