$InCl_3·4H_2O$-Catalyzed Trioxane as a New Methylating Agent for *multi*-Methylated Aromatics Affording Hexamethyl Benzene

Song-Jie Chen and Ruimao Hua*

Department of Chemistry, Tsinghua University, Innovative Catalysis Program, Key Laboratory of Organic Optoelectronics & Molecular Engineering of Ministry of Education, Beijing 100084, China

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Abstract: In the presence of a catalytic amount of $InCl_3·4H_2O$, trioxane was first used as the methylating agent for *multi*-methylated aromatic compounds such as pentamethylbenzene, 1,2,4,5-tetramethylbenzene and 1,3,5-trimethylbenzene to afford hexamethylbenzene in fair to high yields.

Keywords: Hexamethylbenzene, indium chloride, methylating agent, trioxane.

INTRODUCTION

Hexamethyl benzene (HMB) is a simple and important compound used as a high boiling-point solvent in organic reactions and as an intermediate in the fragrance industry. The synthesis, reactivity and application of HMB-coordinated transition metal complexes have been well-studied [1-3]. In addition, the functionalization of HMB [4, 5] or the coordinated HMB [6] *via* activation of C-H bond of methyl group(s) has also become a topic of interest in recent years. Some of the most common methods for the synthesis of HMB are the methylation of pentamethylbenzene (PMB) with MeCl in the presence of $AlCl_3$, the reaction of 1,2,3,4,5-pentamethylbenzene with MeMgBr, and the reaction of 1,2,3,4,5,6-hexabromobenzene with MeMgI. However, these known procedures use methyl halides, which are both toxic and not environmentally-benign, as methylating agents. Therefore, the development of new methylation procedures for the synthesis of HMB remains a topic of interest.

Recently, $InCl_3·4H_2O$ has been applied as a catalyst in various organic transformations [7-9]. Our previous work has disclosed that $InCl_3·4H_2O$ is an efficient catalyst for the reaction of an excess amount of electron-rich aromatic compounds with trioxane to afford diarylated methanes in good yields [10]. In our continuing studies in the application of $InCl_3·4H_2O$ as a catalyst in organic transformations, we found that $InCl_3·4H_2O$ could catalyze trioxane as a new methylating agent in the methylation of *multi*-methylated aromatic compounds. In this letter, we report our new preliminary findings.

As summarized in Scheme **1**, when a mixture of pentamethylbenzene (PMB), 2.0 equiv. of trioxane and $InCl_3·4H_2O$ (5 mol% relative to PMB) in CH_2Cl_2 in a sealed tube was heated with stirring at 80 ^oC for 10h, the GC and GC-MS analyses of the reaction mixture disclosed that PMB was consumed completely, and hexamethylbenzene (HMB) was obtained in 92% GC yield, accompanied with the formation of a small amount of di(pentamethylphenyl) methane and 2,3,4,5,6-pentamethylbenzyl alcohol (entry 1). When $CHCl_3$ and 1,2-dichloroethane (DCE) were used as solvents to replace CH_2Cl_2, the yield of HMB, after heating for 8 h was 83% and 84%, respectively (entries 2-3). However, the use of cyclohexane, DMF and CH_3CN as solvents led to either very low yield of HMB or no reaction occurrence (entries 4-6). Repeating the reaction in $CHCl_3$ and DCE and increasing the reaction temperature to 110 ^oC for 8 h resulted in the formation of HMB in excellent yields, and in the later case, HMB could be isolated in 83% yield by column chromatography (silica gel, eluted by petroleum ether) (entries 7-8). The use of DMF and CH_3CN as solvents resulting in no reaction might be due to the possible reaction occurring between $InCl_3·4H_2O$ and the coordinative solvents to lose the catalytic activity.

In addition, under the reaction conditions of entry 8 of Scheme **1**, the catalytic activity of other acids was also examined. Although PMB conversion reached up to 90%, the selectivity for the formation of HMB was low. For example, when $BiCl_3$ was employed as catalyst, the conversion of PMB was up to 97%, but only trace amount of HMB was formed, the major product was bis-(2,3,4,5,6-pentamethyl-phenyl)methane, which was confirmed by GC-MS [10]. In the case of $H_3PMo_{12}O_{40}·nH_2O$ (14 mg) used, HMB was obtained in 31% yield with 95% conversion of PMB.

In order to evaluate the scope of the present methylation procedure, the reactions of other methylated benzenes with trioxane in the presence of $InCl_3·4H_2O$ were also studied. As shown in Scheme **2**, heating a mixture of 1,2,4,5-tetramethylbenzene (TMB) with 2.0 equiv. of trioxane at 80 ^oC for 8 h resulted in the complete conversion of TMB, however, only a trace amount of HMB was found in the reaction mixture. Increase of the reaction temperature (110 ^oC) could improve the formation of HMB, and in this case, the GC yield of HMB was 18%, and the formation of PMB in 4% GC yield was also observed.

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*Address correspondence to this author at the Department of Chemistry, Tsinghua University, Innovative Catalysis Program, Key Laboratory of Organic Optoelectronics & Molecular Engineering of Ministry of Education, Beijing 100084, China; Fax: +86-10-62771149;
E-mail: ruimao@mail.tsinghua.edu.cn

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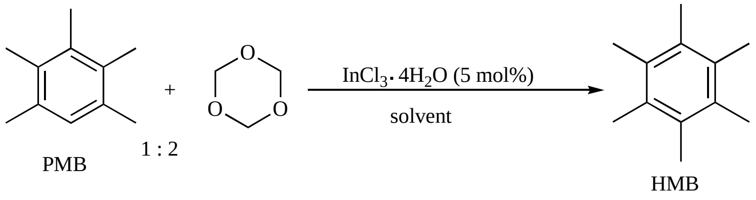
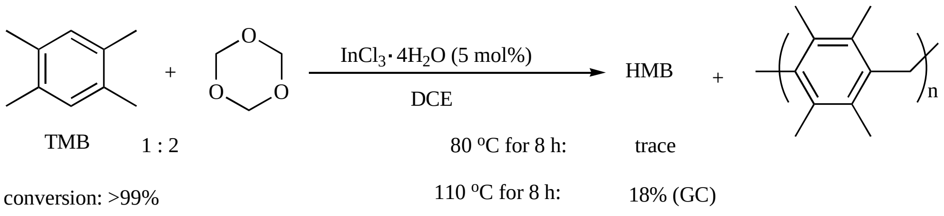


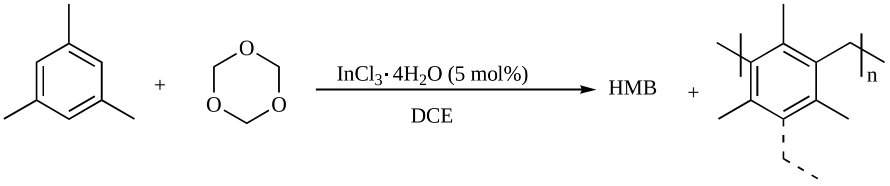
entry	solvent	temp. (°C) / h	conversion of PMB (%)[a]	GC yield of HMB (%)[b]
1	CH_2Cl_2	80 / 10	> 99	92
2	$CHCl_3$	80 / 8	> 99	83
3	DCE	80 / 8	> 99	84
4	cyclohexane	80 / 8	42	< 5
5	DMF	80 / 8	nr	
6	CH_3CN	80 / 8	nr	
7	$CHCl_3$	110 / 8	> 99	93
8	DCE	110 / 8	> 99	(83)

[a] Conversion of PMB was determined by GC.
[b] Number in the parenthesis is isolated yield.

Scheme 1.



Scheme 2.



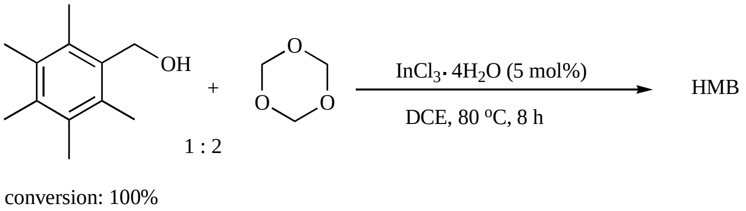
mesitylene : trioxane	temp. (°C) / h	conversion of mesitylene (%)[a]	GC yield of HMB (%)
1 : 2	80 / 8	> 99	trace
1 : 5	110 / 10	> 99	18

[a] Conversion of mesitylene was determined by GC.

Scheme 3.

In the case of 1,3,5-trimethylbenzene (mesitylene) employed, mesitylene was consumed completely with 2.0 equiv. of trioxane at 80 °C for 8 h, or with 5.0 equiv. of trioxane at 110 °C for 10h. A low yield (18% GC) of HMB was obtained in the later case (Scheme **3**).

The reason for the formation of HMB in low yield was considered to be the easy methylidenated polymerization of TMB and mesitylene, which became the predominant reaction under the reaction conditions. In addition, on the basis of the observed results, it is apparent that the low



Scheme 4.

reaction temperature (80 *vs* 110 °C) favors the formation of polymers.

Although the exact mechanism of this new methylation reaction is not yet clear, on the basis of our previous report in which the formation of benzyl alcohol derivatives was the key step for the formation of diarylated methanes [10, 11] and the observation of trace amount of 2,3,4,5,6-pentamethylbenzyl alcohol in the reaction mixture (*vide supra*), we proposed that the formation of 2,3,4,5,6-pentamethylbenzyl alcohol is the key step in the present methylation reaction. Therefore, the reaction of 2,3,4,5,6-pentamethylbenzyl alcohol with trioxane was also examined as shown in Scheme **4**. As expected, 2,3,4,5,6-pentamethylbenzyl alcohol was completely converted into HMB in DCE at 80 °C for 8h.

In summary, we have demonstrated that trioxane can be used as a methylating agent for the methylation of tri-, tetra- and pentamethylbenzene to hexamethylbenzene in fair to high yield in the presence of a catalytic amount of $InCl_3·4H_2O$ [12]. Although the new methylation procedure has its limitations, it is the first example on the use of trioxane as methylating agent, which is more environmentally-friendly compared to traditional ones. Further investigations are underway in our laboratory to develop the methylation procedure using trioxane as methylating agent.

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[12] ^1H and ^{13}C NMR spectra were recorded on JOEL JNM-ECA300 spectrometers at 300 MHz 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 analyses of organic compounds were performed on an Agilent Technologies 1790 GC (with a SGE-OV1701 25m capillary column) instrument. GC-MS was obtained on a Shimadzu GCMS-QP2010S.

A typical procedure for the methylation of PMB with trioxane to afford HMB (Scheme **1**, entry 8)**:** A mixture of PMB (74.1mg, 0.5 mmol), trioxane (90.1, 1.0 mmol) and $InCl_3·4H_2O$ (7.7 mg, 0.025 mmol) in $ClCH_2CH_2Cl$ (0.5 mL) in a screw-capped thick-walled Pyrex tube was heated at 110 °C (oil bath temperature) with stirring for 8 h. After cooling, the reaction was diluted with toluene to 2.0 mL and *n*-$C_{18}H_{38}$ (46.2 mg, as internal standard) was added. The resulting mixture was then analyzed by GC and GC-MS. Volatiles were removed in vacuum and the residue was purified by column chromatography (silica gel, eluted with petroleum ether). HMB (67.3 mg, 0.42 mmol, 83 %) was obtained as white solid. GC analysis of the reaction mixture revealed that HMB was formed in 99% yield. HMB: ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ132.2, 16.9; GCMS *m/z* (% relative intensity): 162 (M^+, 47), 147 (100), 119 (9), 105 (9). 91 (13).