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One-pot solvent-free synthesis of triaryl- and triheteroarylmethanes by Bi(OTf)$_3$-catalyzed Friedel-Crafts reaction of arenes/heteroarenes with trialkyl orthoformates

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ABSTRACT

A convenient, practical and highly efficient one-pot method has been developed for the synthesis of triaryl- and triheteroarylmethane derivatives by Bi(OTf)$_3$-catalyzed Friedel-Crafts alkylation of trialkyl orthoformates in combination with a wide variety of arenes/heteroarenes at room temperature under solvent-free conditions and in an air atmosphere. The methodology offers an operational simplicity, high atom economy and environmentally benign procedure. Furthermore, selected compound **3k** showed promising anti-inflammatory activity with inhibition nitric oxide and did not exhibit significant cytotoxic effects on macrophage cells.

1. Introduction

During the last decade, triaryl- and triheteroarylmethanes have attracted the attention of many scientists due to the broad scope of their biological activities and their significant applications in the dye industry and materials science [1]. For instance, symmetrical triindolylmethanes (TIMs) are present in many products isolated from bacteria and serve as bacterial metabolic and cytotoxic agents [2]. Moreover, they show an affinity for hydride ions and dye materials and are effective frameworks for the construction of very bulky π-acidic phosphine ligands [3]. Tripyrrolylmethanes can potentially be utilized as a starting material for the preparation of dendrimers [4]. Trithienylmethane derivatives find many applications in non-linear optics and conducting polymer [5]. As a result of their biological and synthetic importance, a number of methods for the synthesis of symmetrical triaryl- and triheteroarylmethanes by Lewis acids or BrØnsted acid-catalyzed Friedel-Crafts-type substitution of the three alkoxy groups in a trialkyl orthofortmate have been reported in the literature [1n,4-6]. However, most of the examples reported to date have been limited to reactions of an indole substrate [1n,6]. These suffer from some disadvantages such as the use of high toxicity or corrosiveness of the promoters employed [4,6a-d,6f], high catalyst loading [4,6b,6i], elevated temperature [6a,6b], long duration [6b], low yields of products and special care for moisture/air sensitive reagents [6b,6f].

In the past decade, bismuth(III) triflate has become as an environmentally benign catalyst and has been used as a catalyst for various types of organic transformations in organic synthesis [7]. The catalyst Bi(OTf)$_3$ is highly tolerant to air as well as moisture and associated with low cost which make it attractive as a practical catalyst [7]. As part of our ongoing studies in developing simple, convenient and eco-friendly methods for the synthesis of biologically active compounds [8], we report here the one-pot solvent-free synthesis of triaryl- and triheteroarylmethanes *via* a triple Friedel-Crafts reaction of trialkyl orthoformates with a variety of trimethoxybenzene and heteroarenes including furan, thiophene, pyrrole and indole derivatives using Bi(OTf)$_3$ as catalyst at room temperature under solvent-free conditions and in an air atmosphere. In an effort to discover a lead compound for the development of novel non-steroidal anti-inflammatory agents, the synthesized compounds were further evaluated for their anti-

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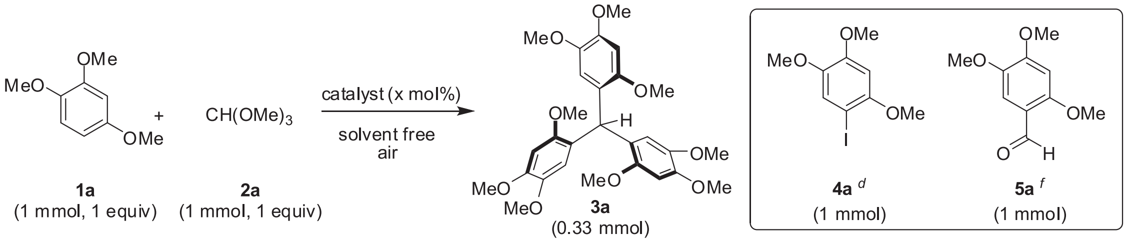
inflammatory effects on the production of inflammatory factors NO and cytotoxicity in activated macrophages.

2. Results and discussion

Initially, a synthetic plan was designed to access symmetrical triaryl- and triheteroarylmethanes mediated by $Bi(OTf)_3$ employing 1,2,4-trimethoxybenzene with trimethyl orthoformate as a model reaction to determine the optimum reaction conditions (Table 1). As anticipated, the reaction in the presence of $Bi(OTf)_3$ (10 mol%) produced the symmetrical polymethoxy substituted triphenylmethane **3a** in excellent yield under solvent-free and air atmosphere at room temperature for 3 h (entry 1). The reaction under nitrogen atmosphere was then performed and gave the desired product **3a** in comparable yield with the case of the reaction under an air atmosphere (entry 2). Increasing reaction temperature to 60 °C afforded the compound **3a** in excellent yield within 1 h (entry 3). By lowering the catalyst loading to 5 mol% (entry 4), the desired product **3a** was also obtained in high yield, however, a longer reaction time was necessary. The effect of various solvents was further studied (entries 5–11). Among the solvents tested, toluene, dichloromethane, dichloroethane and acetonitrile also produced the product **3a** in excellent yield but with longer reaction time (24 h). A lower yield was obtained when using tetrahydrofuran, methanol or water as a solvent (entries 9–11). By comparison to the reaction catalyzed by $Bi(OTf)_3$, the reaction in the presence of molecular iodine (20 mol%) gave the lower yield of **3a** (entries 1 and 12). Using a stoichiometric amount of molecular iodine to catalyze the reaction gave the desired product **3a** and iodination adduct, 5-iodo-1,2,6-trimethoxybenzene (**4a**) in 46% and 45%, respectively (entry 13). Three catalysts, $InCl_3 \cdot 4H_2O$, $Cu(OAc)_2$ and $B(OEt)_3$ which have wide applications in organic synthesis failed to facilitate the reaction transformation (entries 14, 15 and 18). Interestingly, the reaction in the presence of $BF_3 \cdot Et_2O$ (60 mol%) as Lewis acid gave the desired product **3a** in 46% yield. Moreover, 2,4,5-trimethoxybenzaldehyde (**5a**) was isolated in 30% yield (entry 16). Employing $BF_3 \cdot Et_2O$ as stoichiometric amount (1 mmol, 300 mol%) also gave the comparable results. Compounds **3a** and **5a** were obtained in 44% and 29%, respectively (entry 17). A control experiment showed that no reaction was observed in the absence of $Bi(OTf)_3$ even after a long reaction time (24 h) (entry 19). These experiments led to the confirmation that $Bi(OTf)_3$ is highly tolerant to air and is a highly efficient catalyst for the reaction transformation.

To evaluate the scope of the strategy for the synthesis of corresponding triaryl- and triheteroarylmethanes, a variety of trimethoxybenzene as well as heteroarenes such as furan, thiophene, pyrrole and indole derivatives were reacted with trimethyl or triethyl orthoformates in the presence of 10 mol% $Bi(OTf)_3$ at room temperature under solvent-free condition and air atmosphere. The experimental results are summarized in Table 2. The reaction of 1,2,4-trimethoxybenzene employing triethyl orthoformate as alkylating agent also proceeded smoothly to afford the compound **3a** in high yield (entry 2). Compared to 1,2,4- trimethoxybenzene, the more sterically electron-rich arene, 1,3,5-trimethoxybenzene gave a lower yield of the desired adduct **3b** and unusual

Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst	mmol (mol%)	Solvent	Temp. (°C)	Time (h)	Yield [b] (%) of **3a**
1	$Bi(OTf)_3$	0.033 (10)	–	rt	3	>99
2	$Bi(OTf)_3$	0.033 (10)	–	rt	3	>99 [c]
3	$Bi(OTf)_3$	0.033 (10)	–	60	1	>99
4	$Bi(OTf)_3$	0.016 (5)	–	rt	6	80
5	$Bi(OTf)_3$	0.033 (10)	Toluene	rt	24	90
6	$Bi(OTf)_3$	0.033 (10)	CH_2Cl_2	rt	24	>99
7	$Bi(OTf)_3$	0.033 (10)	$ClCH_2CH_2Cl$	rt	24	>99
8	$Bi(OTf)_3$	0.033 (10)	CH_3CN	rt	24	>99
9	$Bi(OTf)_3$	0.033 (10)	THF	rt	24	31
10	$Bi(OTf)_3$	0.033 (10)	MeOH	rt	24	10
11	$Bi(OTf)_3$	0.033 (10)	H_2O	60	24	trace
12	I_2	0.066 (20)	–	rt	3	73
13	I_2	0.33 (100)	–	rt	3	46 (**4a**, 45%) [d]
14	$InCl_3 \cdot 4H_2O$	0.033 (10)	–	rt	24	– [e]
15	$Cu(OAc)_2$	0.033 (10)	–	rt	24	– [e]
16	$BF_3 \cdot OEt_2$	0.20 (60)	–	rt	1	46 (**5a**, 30%) [f]
17	$BF_3 \cdot OEt_2$	1.00 (300)	–	rt	1	44 (**5a**, 29%) [f]
18	$B(OEt)_3$	1.00 (300)	–	rt	24	– [e]
19	–	–	–	rt	24	– [e]

[a] Reaction conditions: **1a** (1.0 mmol, 1 equiv), **2a** (1.0 mmol, 1 equiv), catalyst (0.033 mmol, 10 mol%), under air atmosphere at room temperature.

[b] Isolated yields.

[c] Reaction was carried out under N_2 atmosphere at room temperature.

[d] 5-Iodo-1,2,6-trimethoxybenzene (**4a**) was also isolated in 45%.

[e] No reaction based on TLC analysis.

[f] 2,4,5-trimethoxybenzaldehyde (**5a**) was isolated as a side product.