Tetrahedron 74 (2018) 4373–4380

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

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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ARTICLE INFO

Article history:
Received 29 March 2018
Received in revised form
21 May 2018
Accepted 28 May 2018
Available online 29 May 2018

Keywords:
Triarylmethane
Triheteroarylmethane
Bismuth(III) triflate
Friedel-Crafts reaction
Trialkyl orthoformate

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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https://doi.org/10.1016/j.tet.2018.05.079
0040-4020/

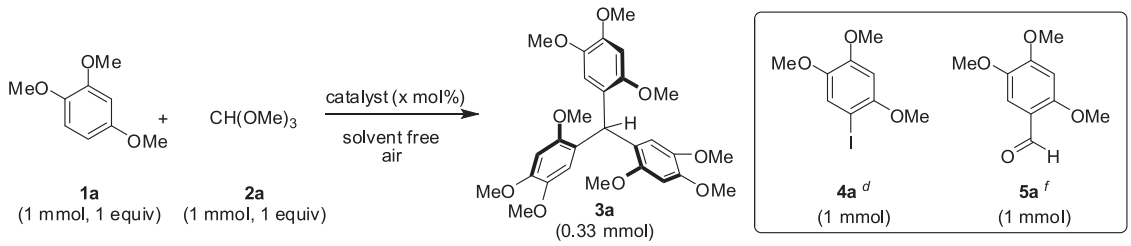
inflammatory effects on the production of inflammatory factors NO and cytotoxicity in activated macrophages.

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

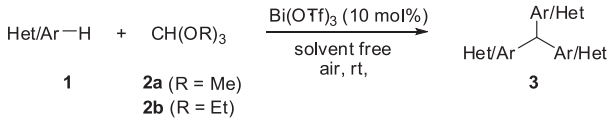
Table 1
Optimization of the reaction conditions.[a]

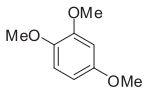
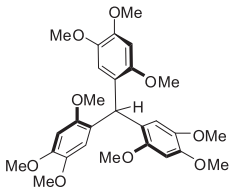
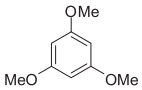
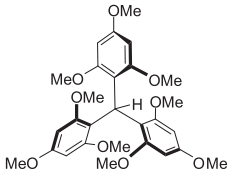
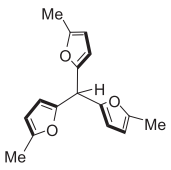
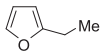
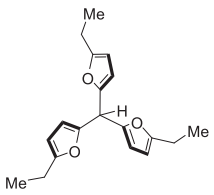
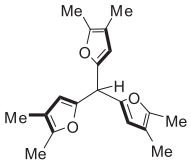
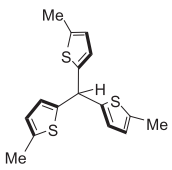
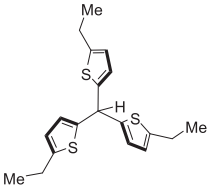
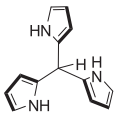


Entry	Catalyst	mmol (mol%)	Solvent	Temp. (°C)	Time (h)	Yield [b] (%) of **3a**
1	$Bi(OTf)_3$	0.033 (10)	–	rt	3	>99
2	$Bi(OTf)_3$	0.033 (10)	–	rt	3	>99 [c]
3	$Bi(OTf)_3$	0.033 (10)	–	60	1	>99
4	$Bi(OTf)_3$	0.016 (5)	–	rt	6	80
5	$Bi(OTf)_3$	0.033 (10)	Toluene	rt	24	90
6	$Bi(OTf)_3$	0.033 (10)	CH_2Cl_2	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.

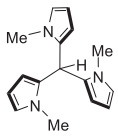
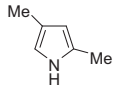
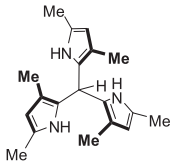
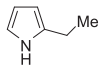
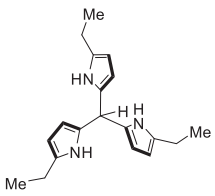
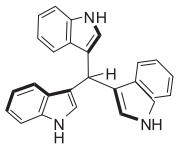
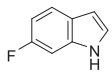
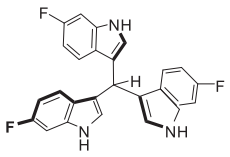
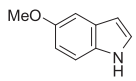
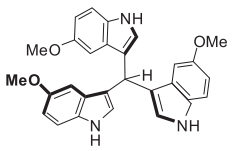
Table 2
$Bi(OTf)_3$-catalyzed reaction of arenes/heteroarenes with trialkyl orthoformates.[a]



Entry	Het/Ar–H (1)	$CH(OR)_3$ (2)	Product		Time (h)	Yield [b] (%)
1		$CH(OMe)_3$		**3a**	3	>99
2		$CH(OEt)_3$		**3a**	3	86
3		$CH(OMe)_3$		**3b**	24	trace
4		$CH(OMe)_3$		**3b**	24	20 (**6**, 39%) [c,d]
5		$CH(OMe)_3$		**3b**	24	22 (**6**, 40%) [c,e]
6		$CH(OEt)_3$		**3b**	24	20 (**6**, 48%) [c,f]
7		$CH(OMe)_3$		**3c**	1	>99
8		$CH(OEt)_3$		**3c**	1	96
9		$CH(OMe)_3$		**3d**	1	>99
10		$CH(OEt)_3$		**3d**	1	93
11		$CH(OMe)_3$		**3e**	1	>99
12		$CH(OEt)_3$		**3e**	1	98
13		$CH(OMe)_3$		**3f**	24	53
14		$CH(OMe)_3$		**3f**	24	59 [d]
15		$CH(OMe)_3$		**3f**	2	64 [e]
16		$CH(OEt)_3$		**3f**	24	45
17		$CH(OMe)_3$		**3g**	24	57
18		$CH(OMe)_3$		**3g**	24	62 [d]
19		$CH(OMe)_3$		**3g**	2	67 [e]
20		$CH(OEt)_3$		**3g**	24	49
21		$CH(OMe)_3$		**3h**	1	– [g]
22		$CH(OMe)_3$		**3h**	1	– [d,g]
23		$CH(OMe)_3$		**3h**	1	– [e,g]
24		$CH(OEt)_3$		**3h**	1	– [g]

(*continued on next page*)

Table 2 (*continued*)

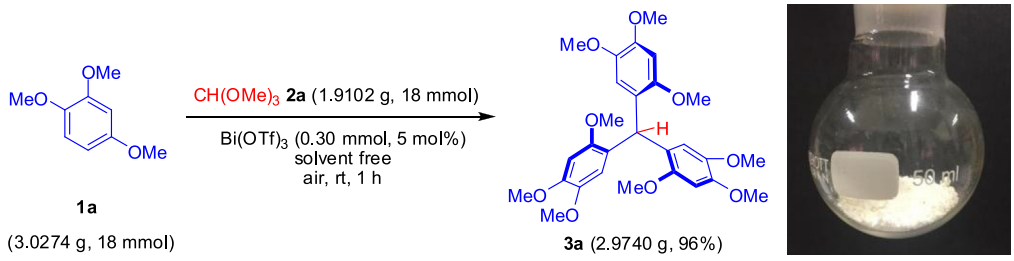
Entry	Het/Ar–H (1)	$CH(OR)_3$ (2)	Product		Time (h)	Yield [b] (%)
25		$CH(OMe)_3$		**3i**	1	32
26		$CH(OMe)_3$		**3i**	1	30 [d]
27		$CH(OMe)_3$		**3i**	1	26 [e]
28		$CH(OEt)_3$		**3i**	1	43
29		$CH(OMe)_3$		**3j**	1	47
30		$CH(OMe)_3$		**3j**	1	49 [d]
31		$CH(OMe)_3$		**3j**	1	39 [e]
32		$CH(OEt)_3$		**3j**	1	>99
33		$CH(OMe)_3$		**3k**	1	39
34		$CH(OMe)_3$		**3k**	1	42 [d]
35		$CH(OMe)_3$		**3k**	1	33 [e]
36		$CH(OEt)_3$		**3k**	1	76
37		$CH(OMe)_3$		**3l**	1	– [g]
38		$CH(OMe)_3$		**3l**	1	87 [h]
39		$CH(OEt)_3$		**3l**	1	76 [h]
40		$CH(OMe)_3$		**3m**	1	64 [h]
41		$CH(OEt)_3$		**3m**	1	58 [h]
42		$CH(OMe)_3$		**3n**	1	93 [h]
43		$CH(OEt)_3$		**3n**	1	82 [h]

[a] Reaction conditions: **1a** (1.0 mmol, 1 equiv), **2a** or **2b** (1.0 mmol, 1 equiv), $Bi(OTf)_3$ (0.033 mmol, 10 mol%), under neat condition at room temperature.
[b] Isolated yields.
[c] Bis(2,4,6-trimethoxyphenyl)methane (**6**) was isolated as a side-product.
[d] The reaction was carried out in the presence of $Bi(OTf)_3$ (0.066 mmol, 20 mol%) at room temperature under neat condition.
[e] The reaction was carried out in the presence of $Bi(OTf)_3$ (0.033 mmol, 10 mol%) at 70 °C.
[f] The reaction was carried out in $ClCH_2CH_2Cl_2$ (1 mL) under reflux for 24 h.
[g] Mixtures of products were observed.
[h] The reaction was carried out in CH_2Cl_2 (1 mL) at room temperature.

bis(2,4,6-trimethoxyphynyl)methane (**6**) was obtained as a side-product in modest yield (entries 4–6). Not only aromatic nucleophiles but also heteroaromatic nucleophiles like 2-methylfuran, 2-ethylfuran as well as 2,3-dimethylfuran were satisfactory in affording trifurylmethane derivatives **3c**, **3d** and **3e** in excellent yields. The use of 2-methyl- and 2-ethylthiophene, which is known to be a poorly reactive necleophile [9], reacted smoothly with trimethyl or triethyl orthoformate under optimized reaction condition (Table 1, entry 1) to give symmetrical trithienylmethane derivatives **3f** and **3g** in modest yields, although a longer reaction time (24 h) was employed to accomplish the reaction (Table 2, entries 13, 16, 17 and 20). Gratifyingly, increasing the catalyst loading to 20 mol% or increasing reaction temperature to 70 °C can increase the chemical yields of products **3f** and **3g** (entries 14–15 and 18–19). Subsequently, pyrrole and its derivatives were tested for the construction of tris(pyrrolyl)methane analogs. Unfortunately, the reaction of unsubstituted pyrrole was unsuccessful, only yielding a complex mixture (entries 21–24). However, the use of substituted pyrroles such as *N*-methylpyrrole, 2,4-dimethylpyrrole and 2-ethylpyrrole reacted smoothly with trimethyl or triethyl orthoformate to afford symmetrical tripyrrolylmethanes **3i**, **3j** and **3k** in moderate to good yields (entries 25–36). $Bi(OTf)_3$-catalyzed the triple Friedel-Crafts-type reactions of trialkyl orthoformates with both reactive and unreactive indoles also proceeded well to provide the compounds **3l**, **3m** and **3n** in high yields, although addition of CH_2Cl_2 as solvent was required in the reaction (entries 37–43).

To demonstrate the scalability and practicality of this method, a gram scale reaction using 1,2,4-trimethoxybenzene (**1a**) (3.0274 g, 18 mmol, 1 equiv) and trimethyl orthoformate (1.9102 g, 18 mmol, 1 equiv) was also performed. Notably, we could reduce the catalyst loading from 10 mol% to 5 mol% without impacting the yield of the reaction (Scheme 1).

The versatility of our method was further tested using a mixture



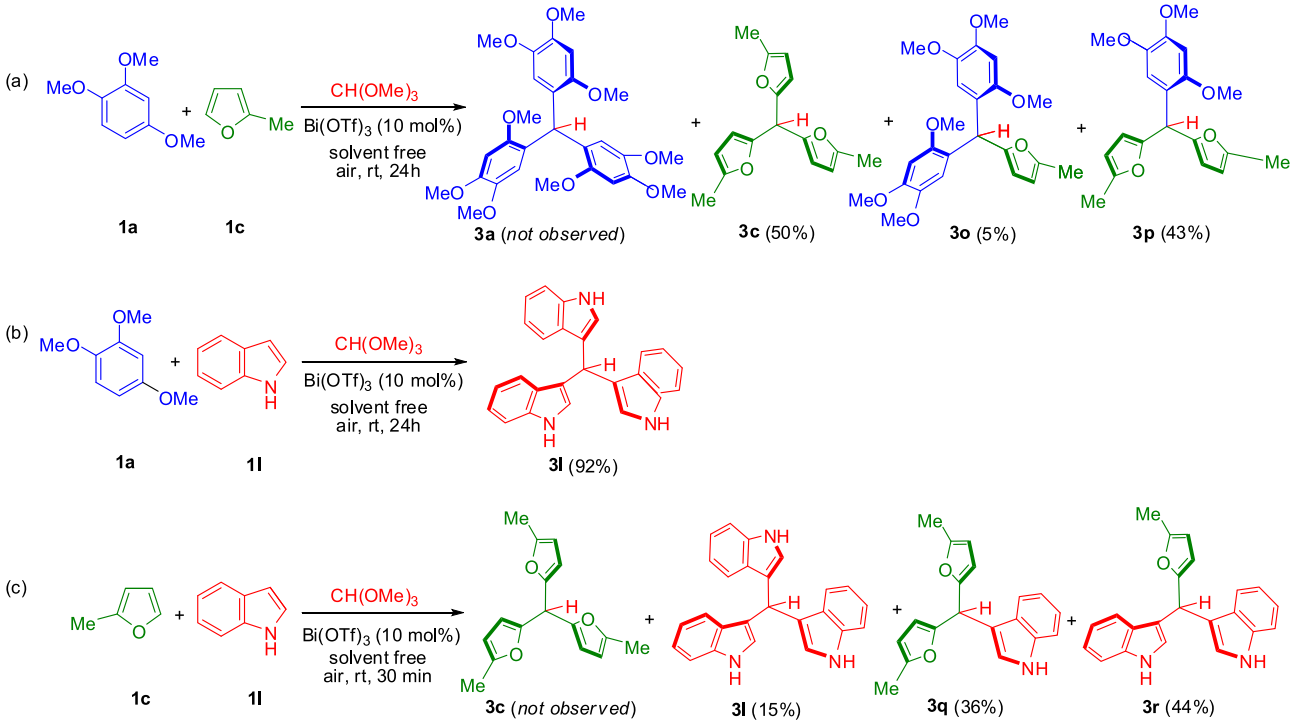
Scheme 1. Gram-scale reaction.

of different arene/heteroarene substrates in the reaction transformation. A series of experiments were performed as outlined in Scheme 2. Initially we found that a competitive reaction between 1,2,4-trimethoxybenzne and 2-methylfuran in the presence of $Bi(OTf)_3$ under neat conditions delivered a mixture of three products, **3c**, **3o** and **3p** in 50%, 5% and 43% yields, respectively (Scheme 2a). Whereas the competition between indole and 1,2,4-trimethoxybenzene gave exclusively compound **3l** as a sole product in very high yield and within 15 min (Scheme 2b). Finally, the reaction employing a combination of 2-methylfuran and indole substrates was also carried out. In this case, the two products derived from two different hetroarene substrates, **3q** and **3r**, were observed in modest yields and only a small amount of **3l** was formed (Scheme 2c). The results shown in Scheme 2 are probably due to the fact that the nucleophilic reactivity of indole is higher than both 2-methylfuran and 1,2,4-trimethoxybenzene.

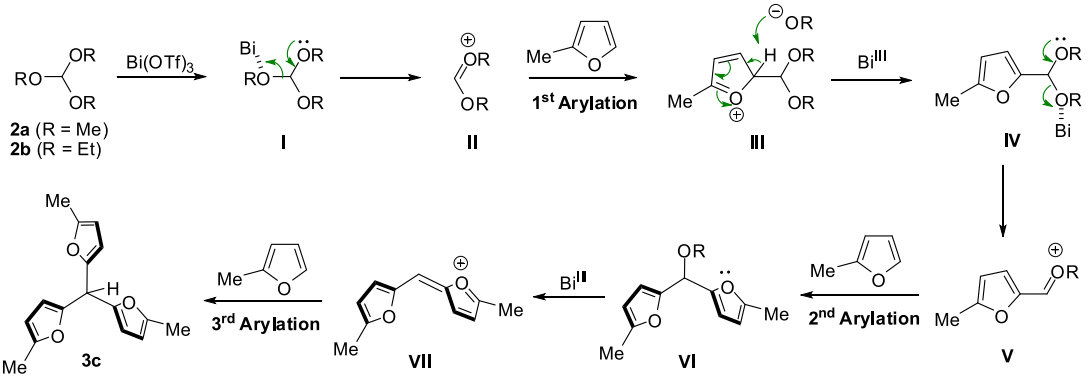
On the basis of the literature information as well as our experimental results, $Bi(OTf)_3$ acts as a Lewis acid and plays a significant role in increasing the electrophilic character of the trialkyl orthoformate [1a-c]. A plausible explanation of the mechanism is depicted in Scheme 3.

Later the cytotoxic activity of the synthesized compounds was evaluated by the determination of cell viability using an MTT assay [8a-b]. The results are shown in Table 3. Most of tested compounds exhibited little to no cytotoxic effect on cells up to a concentration of 50 μM, except for tris[3-indolyl]-6-fluoromethane (**3m**) and tris [3-indolyl]-5-methoxymethane (**3n**). The relative cell viabilities for the latter two compounds were 16.9% and 21.6%, respectively (entries 16 and 17). These results revealed that the substitution with methoxy or fluoro in the indole ring of the triindoylmethane led to a remarkable cytotoxicity to macrophages.

Nitric oxide (NO), a significant pro-inflammatory mediator which is produced by iNOS, has been implicated in several inflammation-related diseases [8a-b,10]. Inhibition of NO production is an important therapeutic target of inflammatory disease. Therefore, the synthesized compounds were evaluated *in vitro* for their inhibitory activity on the production of NO mediators produced by LPS-stimulated RAW 264.7 macrophage cells by the Griess reaction [10]. As shown in Table 3 all of the compounds, except for **3j**, significantly inhibited LPS-induced NO production ($P < 0.05$) when used at 50 μM concentrations. Three compounds (**3k**, **3m** and **3n**) inhibited it by more than 70% as compared to cells treated with LPS alone. Aminoguanidine (50 μM), a specific inhibitor of iNOS activity, was used as the positive control and inhibited induction of



Scheme 2. Competition reaction between two nucleophiles.



Scheme 3. Proposed mechanism for the synthesis of tris(5-methylfuran-2-yl)methane (**3c**).

Table 3
In vitro effects of triaryl- and triheteroarylmethanes on LPS-induced NO production and cell viability [a].

Entry	Compounds	% Cell viability [b]	NO production (inhibition, %) [c,*]	IC_{50} (μM) of NO inhibition[e]
1	Control	100.0 ± 0.0	- ± -	–
2	DMSO (0.2% v/v)	100.8 ± 0.8	- ± -	–
3	LPS (1 μg/mL)	99.0 ± 1.2	0.0 ± 0.0	–
4	AG[d] (50 μM)	97.1 ± 2.2	51.8 ± 1.6	44.5 ± 0.3[f]
5	**3a**	100.9 ± 3.5	17.1 ± 6.9	–
6	**3b**	58.8 ± 4.2	15.9 ± 1.3	–
7	**3c**	97.7 ± 0.5	47.7 ± 3.7	–
8	**3d**	100.8 ± 1.3	42.6 ± 5.1	–
9	**3e**	102.8 ± 2.0	39.8 ± 9.3	–
10	**3f**	99.6 ± 1.7	23.8 ± 6.5	–
11	**3g**	100.9 ± 2.0	21.4 ± 11.9	–
12	**3i**	100.7 ± 2.0	29.3 ± 3.0	–
13	**3j**	100.1 ± 1.2	7.8 ± 11.6	–
14	**3k**	99.2 ± 2.7	70.7 ± 2.9	46.0 ± 3.4
15	**3l**	104.8 ± 1.1	39.9 ± 5.9	–
16	**3m**	16.9 ± 4.5	89.2 ± 6.7	–
17	**3n**	21.6 ± 10.8	82.2 ± 2.2	–
18	**3o**	103.5 ± 5.3	68.1 ± 7.3	–
19	**3p**	98.3 ± 6.1	41.3 ± 7.2	–
20	**3q**	97.0 ± 5.5	28.0 ± 4.0	–
21	**3r**	93.7 ± 5.2	58.48 ± 2.8	–
22	2-ethylpyrrole	100.6 ± 1.9	12.5 ± 3.1	–

*$p < 0.05$ compared to LPS-treated cells.
[a] All data are mean ± SD of at least three independent experiments with triplicate samples.
[b] Cell viability of each treatment was presented as percentage of unstimulated cells (control).
[c] The percentage inhibition of NO production of each treatment (50 μM) was determined in comparison to LPS-stimulated RAW264.7 macrophage cells (LPS) for 24 h.
[d] AG (Aminoguanidine)-a specific inhibitor of iNOS activity.
[e] Concentration of compound was inhibited the production of nitrite with 50%.
[f] Under our experimental conditions.

nitrite level by LPS (51.8 ± 1.6% inhibition). The compound alone and 0.1% (v/v) DMSO did not stimulate nitric oxide production as compared to the control cells. Based on the effects on cell viability and inhibition of NO production shown in Table 3, compound **3k** with a 5-ethylpyrrole moiety could be considered as a lead compound for the further development of iNOS inhibitors for potential anti-inflammatory agents.

3. Conclusions

We have developed a convenient, practical and highly efficient one-pot method for the synthesis of triaryl- and triheteroarylmethanes by $Bi(OTf)_3$-catalyzed Friedel-Crafts reaction of arenes/heeroarenes with trialkyl orthoformates as alkylating agent at room temperature under solvent-free conditions and air atmosphere. The advantages of this method include the broad substrate scope, operational simplicity, high atom economy and the use of inexpensive and environmentally benign catalyst. In addition, the tris(5-ethyl-1H-pyrrol-2-yl)methane (compound **3k**) showed promising anti-inflammatory activity with inhibition NO and did not exhibit significant cytotoxic effects on macrophage cells. The current study provides a clue for the further development of new types non-steroidal anti-inflammatory agents (NSAIDs).

4. Experimental section

4.1. General information

All synthesized compounds were characterized on the basis of 400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR spectroscopic data (BRUKER AVANC), IR spectra (PERKIN ELMER FT/IR-2000s spectrophotometer) and High-resolution mass spectra (HRMS) data (Finnigan MAT 95). ^{1}H NMR and ^{13}C NMR spectra chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) or the residual nondeuterated solvent peak as an internal standard. Radial chromatography on a Chromatotron was

performed using Merck silica gel 60 PF_{254} with $CaSO_4$ $1/2H_2O$ [E. Merck, Darmstadt, Germany] and was activated by heating in an oven at 80 °C for 45 min. Thin layer chromatography (TLC) was performed with Merck silica gel 60 PF_{254} aluminium plate [E. Merck, Darmstadt, Germany]. Melting points were measured using a Melting point apparatus (Griffin) and are uncorrected. All chemicals for synthesis were purchased from commercial sources such as Sigma Aldrich, Germany, Merck, Germany or TCI, Japan and purified if required by a standard technique.

4.2. General procedure for the preparation of compounds **3**

To a solution of arenes/heteroarenes (1.0 mmol, 1 equiv) and trialkyl orthoformates (1.0 mmol, 1 equiv) in a test-tube open to air at room temperature was added $Bi(OTf)_3$ (0.033 mmol, 10 mol%). After the reaction was stirred until completion (TLC analysis), the reaction mixture was quenched with aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then *vacuo*) to give a crude product, which was purified by radial chromatography (SiO_2, 100% hexane to 70% EtOAc/hexane as eluent) to give the corresponding symmetrical triarylmethane **3**.

Spectral data of compounds **3a** [11]., **3c** [12], **3d** [13], **3f** [14], **3i** [15], **3l** [16], **3n** [6h], **3q** [13], and **3r** [17]. were in agreement with those in the literature.

4.2.1. Tris(2,4,5-trimethoxyphenyl)methane (**3a**) [11b]

White solid, yield >99% (from **2a**), 86% (from **2b**); mp 183–187 °C; $R_f = 0.18$ (4:6 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.55$ (s, 3H), 6.42 (s, 3H), 6.23 (s, 1H), 3.89 (s, 9H), 3.67 (s, 9H), 3.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.6, 147.8, 142.7, 124.8, 114.2, 98.7, 57.2, 56.7, 56.0, 36.4$; IR (Nujol-mull): ν_{max} 1603, 1511, 1459, 1395, 1318, 1205, 1180, 1116, 1035, 886, 770 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{34}O_9Na$ $[M+Na]^+$ 537.2101, found 537.2102.

4.2.2. Tris(2,4,6-trimethoxyphenyl)methane (**3b**)

White solid, yield 20% (from **2b**); mp 205–209 °C; $R_f = 0.22$ (3:7 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.28$ (s, 1H), 6.11 (s, 6H), 3.78 (s, 9H), 3.48 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.9, 158.1, 117.2, 92.9, 56.9, 55.1, 28.7$; IR (Nujol-mull): ν_{max} 1591, 1492, 1453, 1412, 1225, 1198, 1149, 1119, 1060, 953, 812 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{34}O_9Na$ $[M+Na]^+$ 537.2101, found 537.2120.

4.2.3. Bis(2,4,6-trimethoxyphenyl)methane (**6**)

White solid, yield 48% (from **2b**); mp 117-108 °C; $R_f = 0.47$ (3:7 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.12$ (s, 4H), 3.87 (s, 2H), 3.79 (s, 6H), 3.73 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.5, 158.9, 112.2, 91.4, 91.3, 56.2, 55.4, 16.9$; IR (Nujol-mull): ν_{max} 1595, 1495, 1455, 1416, 1226, 1203, 1148, 1130, 1059, 949, 808 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}O_6Na$ $[M+Na]^+$ 371.1471, found 371.1487.

4.2.4. Tris[2-(4,5-dimethylfuryl)]methane (**3e**)

Brown oil, yield >99% (from **2a**), 98% (from **2b**); $R_f = 0.61$ (1:9 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.88$ (s, 3H), 5.26 (s, 1H), 2.18 (s, 9H), 1.91 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 149.6, 146.5, 114.5, 110.1, 39.0, 11.4, 9.9$; IR (Nujol-mull): ν_{max} 1674, 1568, 1404, 1222, 1160, 1005, 956, 806, 783 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}O_3Na$ $[M+Na]^+$ 321.1467, found 321.1464.

4.2.5. Tris[2-(5-methylthienyl)]methane (**3f**)

Brown oil, yield 53% (from **2a**), 45% (from **2b**); $R_f = 0.59$ (1:9 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.74$ (br d, $J = 2.9$ Hz, 3H), 6.61 (br d, $J = 2.9$ Hz, 3H), 5.87 (s, 1H), 2.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 145.1, 139.2, 125.4, 124.5, 43.1, 15.4$; IR (Nujol-mull): ν_{max} 1600, 1552, 1482, 1446, 1379, 1260, 1227, 1167, 1042, 967, 800 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}S_3Na$ $[M+Na]^+$ 327.0312, found 327.0311.

4.2.6. Tris[2-(5-ethylthienyl)]methane (**3g**)

Brown oil, yield 57% (from **2a**), 49% (from **2b**); $R_f = 0.63$ (1:9 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.76$ (br d, $J = 3.0$ Hz, 3H), 6.64 (br d, $J = 3.0$ Hz, 3H), 5.89 (s, 1H), 2.82 (q, $J = 7.5$ Hz, 6H), 1.30 (t, $J = 7.4$ Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.0, 144.9, 125.4, 122.8, 43.5, 23.8, 16.0$; IR (Nujol-mull): ν_{max} 1667, 1619, 1456, 1403, 1261, 1223, 1020, 806 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}S_3Na$ $[M+Na]^+$ 369.0781, found 369.0786.

4.2.7. Tris[2-(3,5-dimethylpyrroyl)]methane (**3j**)

Brown oil, yield 47% (from **2a**), >99% (from **2b**); $R_f = 0.66$ (2:8 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$ (br s, 3H, 3xN*H*), 5.72 (br d, $J = 1.9$ Hz, 3H), 5.42 (s, 1H), 2.19 (s, 9H), 1.86 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 125.7, 115.0, 108.9, 32.9, 13.4, 11.0$; IR (Nujol-mull): ν_{max} 3363 (N-H), 1691, 1599, 1509, 1456, 1375, 1260, 1147, 952, 750 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{25}N_3Na$ $[M+Na]^+$ 318.1946, found 318.1957.

4.2.8. Tris[2-(5-ethylpyrroyl)]methane (**3k**)

Brown solid, yield 39% (from **2a**), 76% (from **2b**); mp 139–141 °C; $R_f = 0.44$ (2:8 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (br s, 3H), 5.94 (br t, $J = 2.6$ Hz, 3H), 5.86 (br d, $J = 2.6$ Hz, 3H), 5.42 (s, 1H), 2.58 (q, $J = 7.6$ Hz, 6H), 1.22 (t, $J = 7.6$ Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 133.9, 130.0, 106.4, 104.0, 37.6, 20.9, 13.5$; IR (Nujol-mull): ν_{max} 3344 (N-H), 1684, 1579, 1501, 1428, 1375, 1328, 1177, 1032, 1007, 769 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}N_3$ $[M-H]^+$ 294.1963, found 294.1972.

4.2.9. Tris[3-indolyl]-6-fluoromethane (**3m**)

Orange solid, yield 64% (from **2a**), 58% (from **2b**); mp 205–207 °C; $R_f = 0.55$ (100% CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.94$ (br s, 3H, 3xN*H*), 7.39 (dd, $J = 8.6, 5.4$ Hz), 7.07 (dd, $J = 9.6, 1.9$ Hz, 3H), 6.82–6.77 (m, 6H), 6.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.6$ ($^1J_{CF} = 235.0$ Hz), 136.3, 123.3, 123.1 ($^3J_{CF} = 3.0$ Hz), 120.3 ($^3J_{CF} = 10.0$ Hz), 118.8, 107.6 ($^2J_{CF} = 24.0$ Hz), 97.0 ($^2J_{CF} = 26.0$ Hz), 31.0; IR (Nujol-mull): ν_{max} 3415 (N-H), 1706, 1625, 1496, 1456, 1341, 1304, 1213, 1138, 1089, 951, 836, 804, 749 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{15}F_3N_3$ $[M-H]^+$ 414.1213, found 414.1214.

4.2.10. Bis-[(2,4,5-trimethoxyphenyl)-2-(5-methylfuryl)]methane (**3o**)

Yellow solid, yield 5%; mp 127–129 °C; $R_f = 0.13$ (2:8 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.56$ (br d, $J = 3.2$ Hz, 4H), 6.03 (s, 1H), 5.85 (br d, 1H, $J = 2.8$ Hz), 5.65 (br d, 1H, $J = 2.8$ Hz), 3.90 (s, 6H), 3.75 (s, 6H), 3.72 (s, 6H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.2, 151.4, 150.9, 148.3, 142.9, 122.6, 113.8, 108.4, 105.8, 98.6, 57.1, 56.7, 56.1, 36.6, 13.7$; IR (Nujol-mull): ν_{max} 1721, 1610, 1510, 1464, 1396, 1316, 1260, 1213, 1177, 1108, 1036, 876, 764 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{28}O_7Na$ $[M+Na]^+$ 451.1733, found 451.1739.

4.2.11. Bis[2-(5-methylfuryl)-2,4,5-trimethoxyphenyl]methane (**3p**)

Yellow solid, yield 43%; mp 95–97 °C; $R_f = 0.31$ (2:8 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.76$ (s, 1H), 6.57 (s, 1H), 5.89 (br d, $J = 2.8$ Hz), 5.85 (br d, $J = 2.8$ Hz, 2H), 5.79 (s, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 2.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.4, 151.5, 151.3, 148.9, 143.4, 120.3, 113.8, 108.1, 106.2, 98.4, 57.3, 56.9, 56.4, 37.4, 13.9$; IR (Nujol-mull): ν_{max} 1611, 1561, 1509, 1465, 1397, 1315, 1213, 1174, 1110, 1036, 1022, 871, 783 cm^{-1};

HRMS (ESI) calcd for $C_{20}H_{22}O_5Na$ $[M+Na]^+$ 365.1365, found 365.1360.

4.3. Biological activity evaluation

4.3.1. Cell culture

Murine macrophage cell line RAW 264.7 was provided by. Cells were cultured in DMEM-containing 100 U/mL of penicillin, 100 μg/mL of streptomycin, 4 mM L-glutamine, 25 mM D-glucose, 1 mM sodium pyruvate and 10% heat-inactivated fetal bovine serum (FBS) at 37 °C in humidified air containing 5% CO_2. Cells were subcultured by scrapping.

4.3.2. Measurement of the production of NO

Cells (5 × 105 cells/well) were incubated with tested compound and 1 μg/mL LPS for 24 h. Conditioned media was collected to determine the level of nitrite, an oxidation product of NO. Briefly, nitrite concentration was examined by Griess reagent. The percentage of NO production is expressed as: (nitrite concentration of treated sample/nitrite concentration of LPS treatment) × 100 [10].

4.3.3. Cell viability test using MTT assay

Cell viability was evaluated by MTT assay as described by Srisook et al [10]. This assay is based on the reduction of tetrazolium salt (MTT) to formazan by viable cells containing mitochondrial dehydrogenase activity. Cells were exposed to tested compounds for 24 h and media containing 0.1 mg/mL MTT was added, and further incubated for 4 h. The MTT-formazan was dissolved by DMSO. Absorbance of solubilized formazan solution was measured at 550 nm. The percentage of cell viability is expressed as: (absorbance of treated well/absorbance of control well) × 100.

Acknowledgments

This work was financially supported by a Research Grant from Burapha University through the National Research Council of Thailand (Grant nos. 20/2556 and 60/2557) and the Center of Excellence for Innovation in Chemistry (PERCH-CIC), Commission on Higher Education, Ministry of Education of Thailand. The authors are grateful to Dr. Ron Beckett, Faculty of Science, Burapha University, Thailand for his comments and English proofreading as well as thank to Ms. Petcharat Sawai and Ms. Kanjana Duangkate for valuable technical assistance.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.05.079.

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