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Efficient synthesis of triarylmethanes via bisarylation of aryl aldehydes with arenes catalyzed by silica gel-supported sodium hydrogen sulfate

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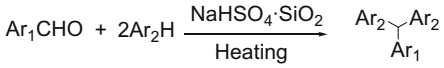
ABSTRACT

An efficient synthesis of triarylmethanes has been developed via bisarylation of aryl aldehydes with arenes catalyzed by silica gel-supported sodium hydrogen sulfate in a solvent-free system. The new method features high yield, mild reaction conditions, and environmental friendliness.

Triarylmethanes are valuable scaffolds that have been used as photochromic agents,[1] dyes,[2] protective groups,[3] and building blocks for dendrimers and NLOs.[4] Additionally, they have maintained an integral part in a number of bioactive compounds and pharmaceuticals.[5] For instance, substituted triarylmethanes have been reported to exhibit antioxidant, antivirus, and antitumor activities.[5a–f] The available methods for the construction of triarylmethane frameworks are based on the bisarylation of an aryl aldehyde using various promoting systems. These promoting systems include (a) acid-catalyzed;[5e,6,7] (b) Grignard reagent-assisted;[5f] (c) microwave-assisted;[8,9] (d) inorganic salts-catalyzed;[10–12] (e) a reductive system of the combination of tris(pentafluorophenyl)borane and polymethylhydrosiloxane;[13] (e) iodine-catalyzed;[14] (f) silica sulfuric acid-catalyzed, a useful system for the synthesis of tri(bis(indolyl) methanes);[15] and (g) silica gel-supported zinc bromide-promoted which features high efficiency and mild conditions.[16] Nevertheless, these approaches are often hindered by the formation of by-products, high catalyst loading, long reaction time, and environmental unfriendliness. As a result, there still exists a need for development of new approaches to the synthesis of triarylmethanes in more efficient and environmental friendly way. Herein, we wish to report an efficient synthesis of triarylmethane via bisarylation of aryl aldehyde catalyzed by silica gel-supported sodium hydrogen sulfate ($NaHSO_4{\cdot}SiO_2$).

Inspired by acid-catalyzed bisarylation of aryl aldehyde, we envisioned that silica gel-supported $NaHSO_4$ (e.g., $NaHSO_4{\cdot}SiO_2$) could be used as a useful acidic reagent for this transformation (Scheme 1). Due to the nature of its environmental friendliness, low cost, and easy preparation,[17] $NaHSO_4{\cdot}SiO_2$ has gradually become a popular reagent in organic synthesis, and it has therefore been widely used in a variety of organic transformations such as nitration, nitrosation, oxidation, halogenation, and coupling of indoles.[18] Recently, we also found that it was a useful reagent for debenzylation of aromatic benzyl ethers.[19]

In an exploratory study, a reaction of 4-methoxybenzaldehyde (**1a**) and thiophene (**2**) in the presence of $NaHSO_4{\cdot}SiO_2$ in $CHCl_3$ was carried out. It was found that the reaction proceeded as expected, but in moderate yield (Table 1, entry 1, 62%). Optimization of reaction conditions revealed that the reaction efficiency was highly solvent dependent. No reaction occurred in CH_2Cl_2, indicating that the lower boiling point of CH_2Cl_2 may account for the result (entry 2). This hypothesis can be further supported by the result obtained in C_4Cl_4 (Table 1, entry 3, 64% yield). The reaction also did not occurr in polar solvent, such as DMF, THF, and 1,4-dioxane (entries 4–6). Among solvents probed, the highest yield was achieved in thiophene (entry 8, in this entry thiophene served as both the reactant and the solvent), which implied that the



Scheme 1. Bisarylation of aryl aldehydes to produce triarylmethanes.

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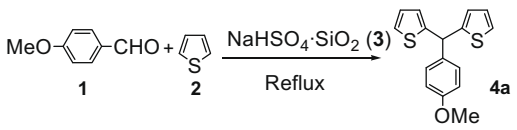
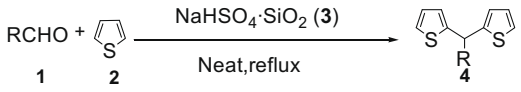
Table 1
Optimization of reaction conditions of thiophene with 4-methoxybenzaldehyde catalyzed by $NaHSO_4{\cdot}SiO_2$[a]



Entry	**2** (mL)	**3** (mg)	Solvent[a]	*t* (h)	Yield[b] (%)
1	0.4	500	$CHCl_3$	7	62
2	0.4	500	CH_2Cl_2	7	NR[c]
3	0.4	500	CCl_4	7	64
4	0.4	500	DMF	7	NR
5	0.4	500	THF	7	NR
6	0.4	500	1,4-Dioxane	7	NR
7	0.4	500	Toluene	7	47
8	3	500	Neat[d]	3	73
9	**3**	**200**	**Neat**	**3**	**76**
10	3	100	Neat	5	74

[a] **1** (1 mmol) and solvent (5 mL) were used unless specified, the content of $NaHSO_4{\cdot}SiO_2$ (1 g, 2.5 mmol of $NaHSO_4$ on SiO_2).
[b] Isolated yield.
[c] NR stands for no reaction.
[d] Neat stands for solvent-free system.

Table 2
The reaction of thiophene with various aldehydes in the presence of $NaHSO_4{\cdot}SiO_2$[a]



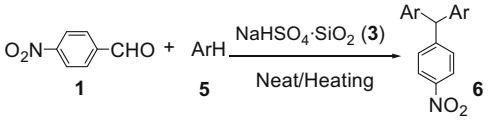
Entry	**1**	R (1 mmol)	*t* (h)	**4**	Mp (°C)	Yield[b] (%)
1	**1a**	4-MeO–C_6H_4	3	**4a**	88–90	76
2	**1b**	3-NO_2–C_6H_4	3	**4b**	72–74	85
3	**1c**	4-NO_2–C_6H_4	2	**4c**	87–89	84
4	**1d**	4-Br–C_6H_4	2.5	**4d**	62–64	84
5	**1e**	C_6H_5	2.5	**4e**	73–74	82
6	**1f**	3-HO–C_6H_4	3	**4f**	NA[c]	66
7	**1g**	3,4-(OCH_2O)–C_6H_3	3.5	**4g**	94–96	64
8	**1h**	3-MeO–4-HO–C_6H_3	5	**4h**	59–61	44[d]
9	**1i**	3-HO–4-MeO–C_6H_3	5	**4i**	66–68	39[e]
10	**1j**	2-Thienyl	6	**4j**	50–51	71
11[f]	**1k**	H	7	**4k**	46–47	58

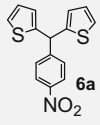
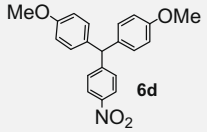
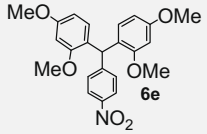
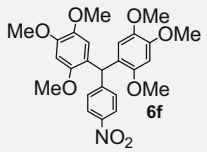
[a] Aldehyde (1 mmol), thiophene (3 mL) and $NaHSO_4{\cdot}SiO_2$ (200 mg, 0.5 mmol of $NaHSO_4$ on SiO_2) were used unless specified.
[b] Isolated yield.
[c] NA (not available), the product is liquid.
[d] Recovered 31% of **1h**.
[e] Recovered 27% of **1i**.
[f] 7 mL of thiophene was used, and the aldehyde in this entry was *para*-formaldehyde.

reaction could proceed in a solvent-free system. Next, the effect of the catalyst loading was tested. A good yield was achieved when a median amount of catalyst loading was used (entry 9). Higher catalyst loading did not improve the yield (entry 8). Reducing the use of the amount of $NaHSO_4{\cdot}SiO_2$ slightly deteriorated the reaction efficiency in terms of product yield and reaction time (entry 10).

The optimized conditions were used to test a range of aldehydes (Table 2). Thiophene was combined with various substituted benzaldehydes in the presence of $NaHSO_4{\cdot}SiO_2$ and the reaction was carried out at reflux (85 °C). It was demonstrated that the reaction of the aldehydes with electron-withdrawing groups such as 3-nitrobenzaldehyde, 4-nitrobenzaldehyde, and 4-bromobenzaldehyde went to completion in less than 3 h to afford the expected triarylmethanes in good yields (entries 2–4). However, the reaction of those aldehydes with electron-donating groups such as 3-hydroxy-

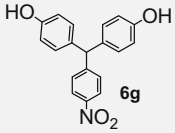
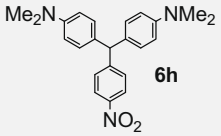
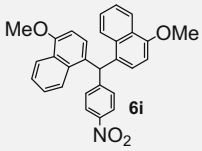
Table 3
Bisarylation of 4-nitrobenzaldehyde with various arenes (ArH) to form triarylmethanes[a]



Entry	Ar	*T* (°C)	*t* (h)	6	Mp (°C)	Yield[b] (%)
1	Thienyl	Reflux	2	 **6a or 4c**	87–89	84
2	4-Me–C_6H_4	Reflux	4	—	—	NR[c]
3	2,4-Me_2–C_6H_3	Reflux	4	—	—	NR
4	4-MeO–C_6H_3	115 130	5 5	 **6d**	47–49	Trace 82
5	2,4-$(MeO)_2$–C_6H_3	115	3	 **6e**	148–149	79
6	2,4,5-$(MeO)_3$–C_6H_2	115	3	 **6f**	123–124	95

(*continued on next page*)

Table 3 (*continued*)

Entry	Ar	*T* (°C)	*t* (h)	6	Mp (°C)	Yield[b] (%)
7	4-HO–C_6H_4	130	5	 **6g**	NA[d]	39[e]
8	4-(Me_2N)–C_6H_4	130	4	 **6h**	182–183	84
9	4-Methoxynaphthyl	130	3	 **6i**	132–134	82

[a] **1** (1 mmol), arene (6 mmol), and $NaHSO_4{\cdot}SiO_2$ (200 mg, 0.5 mmol of $NaHSO_4$ on SiO_2) were used.
[b] Isolated yield.
[c] NR stands for no reaction.
[d] NA (not available), the product is liquid.
[e] 39% of **6g** and 44% of regioisomer 2-hydroxyphenyl-4-hydroxyphenyl-4-nitrophenylmethane.

benzaldehyde, piperonal, vanilline and isovanilline led to lower reaction yields and required longer time as well (entries 6–9). In some cases the reaction did not reach completion even after a prolonged reaction time. For example, the reaction of vanilline after 5 h provided the desired product **4h** in 44% yield along with 31% of unreacted aldehyde **1h** (entry 8), and reaction of isovanilline with thiophene afforded **4i** in 39% yield along with 27% of unreacted aldehyde **1i** (entry 9). Notably, triheteroarylmethanes could also be prepared using this method as trithienylmethane **4j** was afforded in 71% yield (entry 10). Additionally, the reaction of *p*-formaldehyde with thiophene afforded dithiophen-2-ylmethane in 58% yield, but with lower efficacy in term of reaction time and yield (entry 11).

We finally examined the scope of the arenes (Table 3).[20] The results indicated that electronic effect played a major role in the arene substrates. The reaction of an electron-rich arene thiophene proceeded in good yield (entry 1). No reaction took place when toluene and 1,3-xylene were used (entries 2 and 3). A reaction of 4-nitrobenzaldehyde with anisole in the presence of $NaHSO_4{\cdot}SiO_2$ proceeded smoothly at 130 °C in good yield (82%), but only a trace amount of desired product was observed at a slightly lower temperature of 115 °C (entry 4). Substrates such as 2,4-dimethoxybenzene and 1,2,4-trimethoxybenzene bearing more electron-rich groups significantly produced the products at a lower temperature of 115 °C and in a shorter reaction time (compared with substrate anisole of entry 4) with yields of 79% and 95%, respectively (entries 5 and 6). However the reaction for phenol afforded a mixture of the normal product and a regioisomer (entry 7). Notably, the naphthalene derivative was also prepared using substrate 1-methoxynaphthalene in a good yield (entry 9).

In summary, a new approach to access multi-substituted triarylmethanes has been developed via a bisarylation of various aryl aldehydes with electron-rich arenes in the presence of $NaHSO_4{\cdot}SiO_2$. This new approach features high yield, mild reaction conditions, and environmental friendliness, and proves to be an efficient method for the synthesis of valuable triarylmethane derivatives.

Acknowledgements

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Supplementary data

Supplementary data (detailed experimental procedures and the analytical data of all final products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.157.

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19. Zhou, L.; Wang, W.; Zuo, L.; Yao, S.; Wang, W.; Duan, W. *Tetrahedron Lett.* **2008**, *49*, 4876.
20. The preparative procedure of **4a** is given as a representative example of general procedure (Table 1, entry 9). To a suspension of 4-methoxybenzaldehyde (**1a**, 136 mg, 1 mmol) and thiophene (**2**, 3 mL) was added $NaHSO_4{\cdot}SiO_2$ (**3**, 200 mg, 0.5 mmol of $NaHSO_4$ on SiO_2). The reaction mixture was stirred and refluxed for 3 h under an argon atmosphere. The resulting mixture was cooled to room temperature and evaporated to dryness on vacuum. The residue was purified by silica gel column chromatography (200–400 mesh silica gel, 1:10 hexane/ethyl acetate) to afford (4-methoxyphenyl)-bisthienylmethane (**4a**) as white solid (218 mg, 76%). Mp: 88–89 °C. Spectral data of **4a**: ^{1}H NMR ($CDCl_3$) δ: 3.82 (s, 3H), 5.84 (s, 1H), 6.84 (d, 2H, J = 3.2 Hz), 6.88 (d, 2H, J = 8.4 Hz), 6.95 (dd, 2H, J_1 = 3.6 Hz, J_2 = 4.8 Hz), 7.22 (d, 2H, J = 5.2 Hz), 7.24 (d, 2H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 46.8, 55.3, 113.9, 124.6, 125.9, 126.6, 129.4, 136.1, 148.2, 158.7. HRMS (EI) calcd for $C_{16}H_{14}OS_2$ 286.0486, found: 286.0478.