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$InBr_3$: A Versatile Catalyst for the Different Types of Friedel−Crafts Reactions

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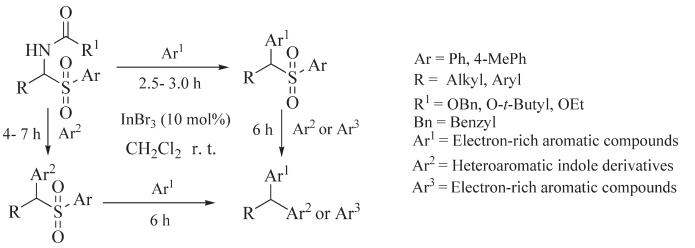

Mild and efficient $InBr_3$-catalyzed Friedel−Crafts alkylation of heteroaromatic or electron-rich aromatic compounds with α-amido sulfones at room temperature in CH_2Cl_2 has been developed. The products undergo further Friedel−Crafts alkylation with heteroaromatic or electron-rich aromatic compounds leading to unsymmetrical or bis-symmetrical triaryl methanes in good yield. α-Amido sulfones are employed for the synthesis of the unsymmetrical and bis-symmetrical triaryl methanes. The use of mild reaction condition, low catalytic loading, and high yield are the advantages of the present procedures.

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Introduction

Friedel−Crafts alkylation is one of the most important C−C bond-forming reactions in organic chemistry.[1] These reactions are usually assisted by either protic acid or Lewis acid catalyst. Indoles and many of its derivatives are present in numerous substances commonly found in nature,[2] as well as in the compounds that show pharmacological and biological activities.[3] The introduction of functionalized alkyl framework at the 3-position in the indole system is a common practice directed to the synthesis of biologically active compounds.[4] A variety of methods have been explored for the Friedel−Crafts alkylation of indole due to its electron-rich nature.[5]

Recently several workers have demonstrated that α-amido sulfones **1** are useful precursors of *N*-acyliminium ions **2** that can further react with several nucleophiles such as allylsilanes, silyl ketene acetals, trimethylsilyl cyanide, and electron-rich aromatics leading to the corresponding adducts **3** (Scheme 1).[6] Petrini and co-workers have demonstrated that the Friedel−Crafts reactions of heteroaromatic indoles with

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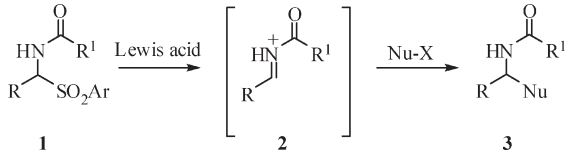
SCHEME 1

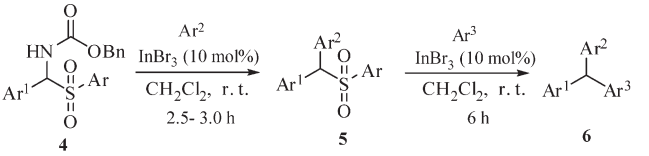


α-amido sulfones catalyzed by montmorillonite K-10 give the unexpected 3-(1-arylsulfonylalkyl)indoles.[7] Moreover 3-(1-arylsulfonylalkyl)indoles have further scope for various synthetic transformations.[8]

In recent years the utility of indium salts as Lewis acids in organic synthesis has received a great deal of attention due to the relatively low toxicity, stability in air and water, and strong tolerance to oxygen- and nitrogen-containing substrates.[9] The application as Lewis acid catalyst to fundamental reactions such as Diels−Alder,[10] Friedel−Crafts,[11] Mukaiyama aldol,[12] and Sakurai−Hosomi allylation reactions[13] has been extensively investigated.[14] In continuation of the development of useful synthetic methodology for C−C bond-forming reactions,[15] we report herein an efficient $InBr_3$-catalyzed Friedel−Crafts alkylation of heteroaromatic or electron-rich aromatic compounds with α-amido sulfones. The products undergo further Friedel−Crafts alkylation with heteroaromatic or electron-rich aromatic compounds giving rise to triaryl methanes.

Triaryl methanes display interesting properties and have received a great deal of attention as leuco dyes,[16] photochromic agents,[17] suitable building blocks for generating dendrimers,[18] and substrates for theoretical[19] and biological[20] studies. While many methods have been reported for the preparation of symmetrical triaryl methanes,[21] the synthesis of unsymmetrical derivatives is far less studied.[22−24] We describe here a broad scope of $InBr_3$-catalyzed Friedel−Crafts alkylations that allow the selective preparation of structurally diverse triaryl methanes through sequential reactions with same or different electron-rich aromatic compounds (Scheme 2; Table 1).

SCHEME 2



Result and Discussion

We have carried out the reaction of α-amido sulfone **4** with heteroaromatic indole **8** in CH_2Cl_2 in the presence of molecular iodine that produces the desired 3-(1-arylsulfonylalkyl)-indole in 58% yield (entry 1). In the absence of any catalyst no product could be detected (entry 2). Then the Lewis acids such as $ZrOCl_2 \cdot 8H_2O$, $Rh(acac)_3$, $Co(acac)_3$, $In(acac)_3$, and $InBr_3$ were screened (entries 3−7). $InBr_3$ (10 mol %) is found to be the most effective catalyst (entry 7). The effect of various solvents also has been studied. CH_2Cl_2 is found to be the solvent of choice in terms of yield and reaction time (entry 12).

On the basis of the optimized reaction conditions, the scope of the Friedel−Crafts alkylation reaction is evaluated and the results are outlined in Table 2. The α-amido sulfone (R = CO_2Et, Ar = Ph, R^1 = Ph) is reacted with a variety of indoles (**11a−e**) to give the Friedel−Crafts alkylation products in good yield. The methyl group at the 2-position of indoles (entry 3 and 6) gives less yield than in case of the reaction of entry 1 because of the steric hindrance exerted by the methyl group. The reactions of 5-methoxy indole (entry 4) or methyl

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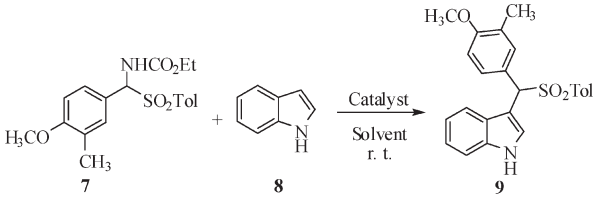
TABLE 1. Friedel−Crafts Alkylation of Heteroaromatic Indoles with α-Amido Sulfones under Various Reaction Conditions[a]

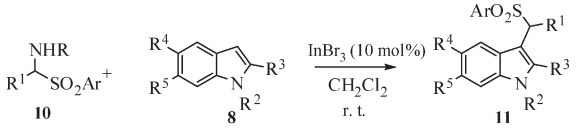


7 8 9

entry	catalyst (mol %)	solvent	reaction time (h)	isolated yield (%)[b]
1	I_2 (20)	CH_2Cl_2	6	58
2		CH_2Cl_2	12	NR
3	$ZrOCl_2 \cdot 8H_2O$ (10)	CH_2Cl_2	8	63
4	$Rh(acac)_3$ (10)	CH_2Cl_2	12	NR
5	$Co(acac)_3$ (10)	CH_2Cl_2	12	NR
6	$In(acac)_3$ (10)	CH_2Cl_2	12	NR
7	$InBr_3$ (10)	CH_2Cl_2	4	89
8	$InBr_3$ (3)	CH_2Cl_2	10	67
9	$InBr_3$ (5)	CH_2Cl_2	8	73
10	$InBr_3$ (15)	CH_2Cl_2	4	89
11	$InBr_3$ (20)	CH_2Cl_2	4	90
		$CHCl_3$	5	70
		1,4-dioxane	6	83
12	$InBr_3$ (10)	THF	8	61
		1,4-dioxane:H_2O (3:1)	10	44
		MeOH	7	40
		H_2O	12	trace

[a]Reaction conditions: α-amido sulfone (1.0 mmol), heteroaromatic indole (1.1 mmol), and solvent (2.0 mL) at r.t. [b]Yield of isolated product after flash column chromatography.

TABLE 2. Friedel−Crafts Alkylation of Heteroaromatic Indoles with α-Amido Sulfones Catalyzed by $InBr_3$[a]



10 8 11

R = CO_2Bn, CO_2*t*-Butyl, CO_2Et
R^1 = Aryl, alkyl Ar = Ph, 4-MePh

8a: $R^2 = R^3 = R^4 = R^5 = H$
8b: R^2 = Me, $R^3 = R^4 = R^5 = H$
8c: R^3 = Me, $R^2 = R^4 = R^5 = H$
8d: R^4 = MeO, $R^2 = R^3 = R^5 = H$
8e: $R^5 = CO_2$Me, $R^2 = R^3 = R^4 = H$

	α-amido sulfone **10**						
entry	R^1	R	Ar	indole **8**	product **11**	reaction time (h)	isolated yield (%)[b]
1	Ph	CO_2Et	4-MePh	**8a**	**11a**	6	83
2	Ph	CO_2Et	4-MePh	**8b**	**11b**	6	76
3	Ph	CO_2Et	4-MePh	**8c**	**11c**	7	80
4	Ph	CO_2Et	4-MePh	**8d**	**11d**	6	78
5	Ph	CO_2Et	4-MePh	**8e**	**11e**	7	75
6	Ph	CO_2Et	Ph	**8c**	**11f**	7	78
7	Ph	CO_2t-Butyl	4-MePh	**8a**	**11a**	6	61
8	Ph	CO_2Bn	4-MePh	**8a**	**11a**	6	68
9	4-MePh	CO_2Et	4-MePh	**8a**	**11g**	5	84
10	4-MeOPh	CO_2Et	4-MePh	**8a**	**11h**	5	86
11	3-Me, 4-MeOPh	CO_2Et	4-MePh	**8a**	**11i**	4	90
12	4-ClPh	CO_2Et	4-MePh	**8a**	**11j**	6	83
13	3-ClPh	CO_2Et	4-MePh	**8a**	**11k**	6	80
14	2-ClPh	CO_2Et	4-MePh	**8a**	**11*l***	7	76
15	C_6H_{11}	CO_2Et	4-MePh	**8a**	**11m**	6	73

[a]Reaction conditions: α-amido sulfone (1.0 mmol), indole (1.1 mmol), $InBr_3$ (0.1 mmol), and CH_2Cl_2 (2.0 mL) at r.t. [b]Yield of isolated product after flash column chromatography.

indole-6-carboxylate (entry 5) with α-amido sulfone (R = CO_2Et, Ar = Ph, R^1 = Ph) produce corresponding 3-(1-arylsulfonylalkyl)indoles in 78% and 75% yield, respectively.

Indole **8a** is used as a substrate to react with various α-amido sulfones for the Friedel−Crafts alkylation reactions (Table 2, entries 7−15). The alkoxy group in the carbamoyl moiety in α-amido sulfones plays an important role for the yield of product. Among the alkoxy groups OEt, O-*tert*-butyl, and OBn in α-amido sulfones (entries 1, 6 and 7), the ethyloxy (OEt) group is found to give the best result (entry 1). The α-amido sulfones with an electron-donating group attached to the benzene ring are able to undergo Friedel−Crafts alkylation

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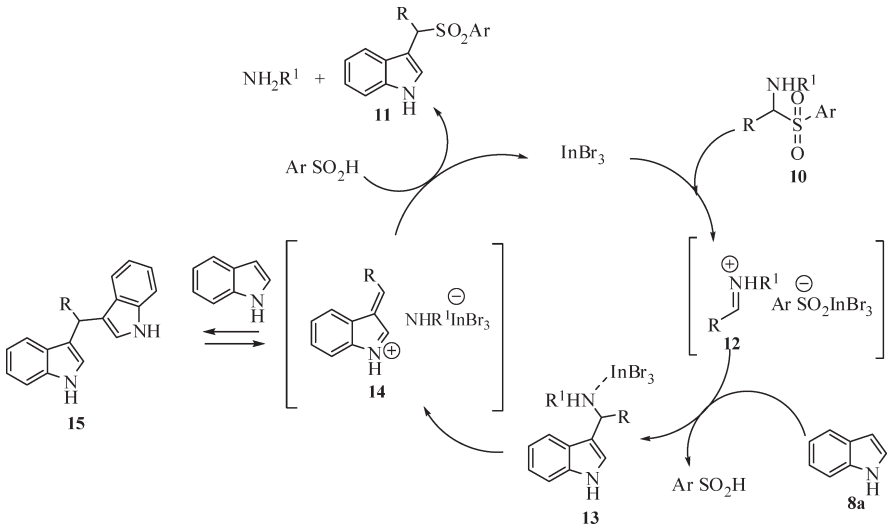

FIGURE 1. Plausible mechanism of $InBr_3$-catalyzed Friedel−Crafts alkylation of α-amido sulfones with indoles.

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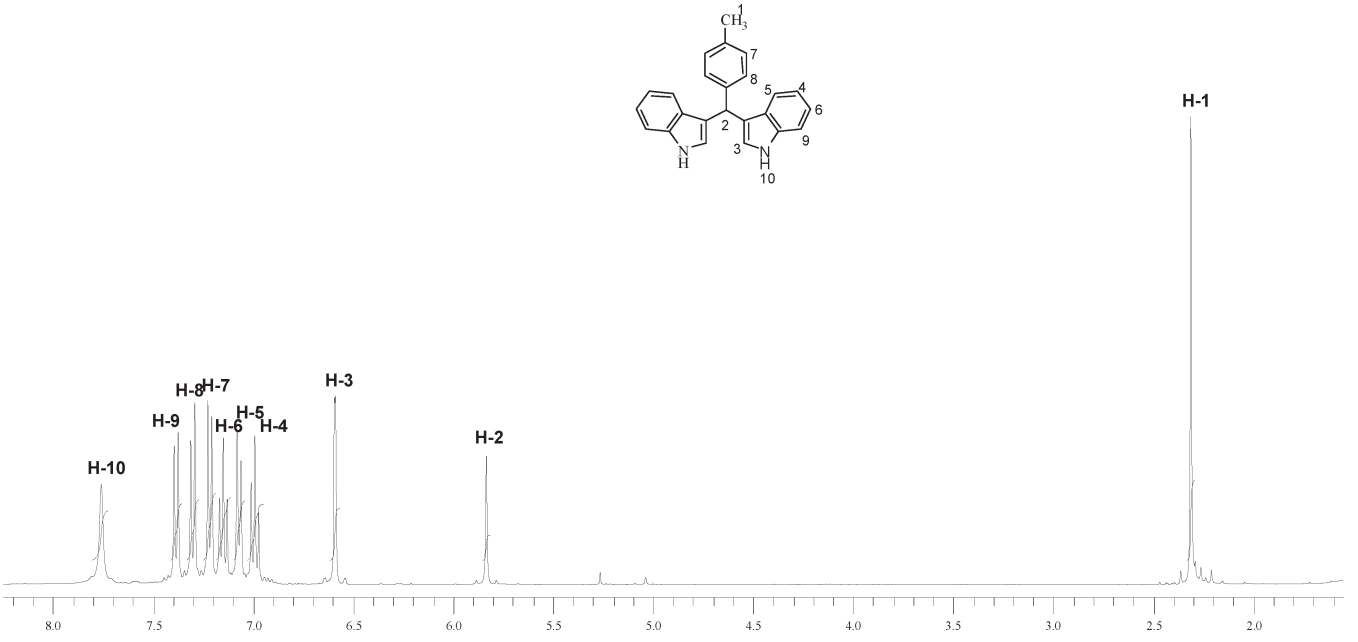

FIGURE 2. ^{1}H NMR of bis-indole **15** (R = 4-MePh).

smoothly and generate the corresponding products in very good yield (entries 9−11). The reactions of *p*-, *m*-, and *o*-chloro-α-amido sulfones with indole **8a** give the corresponding 3-(1-arylsulfonylalkyl)indoles in 83%, 80%, and 76% yield, respectively (entries 12−14). The *o*-chloro isomer indicates slight steric effects that are responsible for the lower yield (entry 14). Cyclohexyl α-amido sulfone brings about the corresponding 3-(1-arylsulfonylalkyl)indole derivative in good yield (entry 15).

A plausible mechanism for the formation of **11** may start from the *N*-acyliminium ion **12** that is formed by elimination of arenesulfinic acid from the α-amido sulfone **10** by the action of $InBr_3$. Reaction of the strong electrophile **12** with indole **8a** gives the Fredel−Crafts product **13** (Figure 1). $InBr_3$ catalyzes the elimination of carbamate from **13** leading to the second iminium ion **14**.[25] The iminium ion **14** then reacts with indole **8a** in a second Fredel−Crafts reaction giving rise to bis-indole **15** through reversible reaction. Formation of bis-indole **15** has been observed during the course of the reaction that completely disappeared at the end of the reaction. After 1.0 h of reaction time **15** (R = 4-MePh) was isolated and characterized by NMR analysis (see Figure 2 and the Supporting Information). The arenesulfinic acid ($ArSO_2H$) reacts with the second iminium ion **14** to afford the desired product **11** (Figure 1).

We have further examined the scope of the Friedel−Crafts alkylation reactions using α-amido sulfones **16** with other electron-rich aromatic compounds **17** and the results are summarized in Table 3. The α-amido sulfone (R = Ph, Ar = 4-MePh) was treated with 1,2,4-trimethoxybenzene **17a** to afford the corresponding diarylsulfone **18a** in excellent yield

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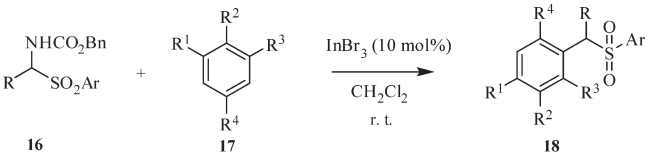
TABLE 3. Friedel–Crafts Alkylation of Electron-Rich Aromatic Compounds with α-Amido Sulfones Catalyzed by $InBr_3$[a]



17a: $R^1 = R^2 = R^4 = OCH_3$, $R^3 = H$
17b: $R^1 = R^3 = OCH_3$, $R^2 = R^4 = H$
17c: $R^1 = R^2 = R^3 = OCH_3$, $R^4 = H$
17d: $R^1 = R^3 = R^4 = OCH_3$, $R^2 = H$

	α-amido sulfone **16**				
entry	Ar	R	arene **17**	product **18**	isolated yield (%)[b,c]
1	4-MePh	Ph	**17a**	**18a**	92
2	4-MePh	Ph	**17b**	**18b**	80
3	4-MePh	Ph	**17c**	**18c**	87
4	4-MePh	Ph	**17d**	**18d**	90
5	Ph	Ph	**17a**	**18e**	86
6	Ph	4-MeOPh	**17a**	**18f**	89
7	4-MePh	4-MePh	**17a**	**18g**	90
8	4-MePh	4-MeOPh	**17a**	**18h**	92
9	4-MePh	3-Me,4-MeOPh	**17a**	**18i**	92
10	4-MePh	4-NO_2Ph	**17a**	**18j**	87
11	4-MePh	4-ClPh	**17a**	**18k**	90
12	4-MePh	3-ClPh	**17a**	**18l**	87
13	4-MePh	2-ClPh	**17a**	**18m**	83
14	4-MePh	$PhCH_2CH_2$	**17a**	**18n**	85
15	4-MePh	C_6H_{11}	**17a**	**18o**	81
16	4-MePh	$(CH_3)_2CHCH_2$	**17a**	**18p**	79

[a]Reaction conditions: α-amido sulfone (1.0 mmol), aromatic compounds (1.1 mmol), $InBr_3$ (0.1 mmol), and CH_2Cl_2 (2.0 mL) at r.t. [b]Yield of isolated product after flash column chromatography. [c]All the reaction times were 2.5 h except for entries 2, 6, 11, and 14–16 that took 3.0 h.

(entry 1). The synthetic utility of the method is further demonstrated by the reaction of α-amido sulfone (R = Ph, Ar = 4-MePh) with electron-rich aromatic compounds such as 1,3-dimethoxy-, 1,2,3-trimethoxy-, and 1,3,5-trimethoxybenzene for formation of aryl sulfones (entries 2–4). The reactions of various α-amido sulfones containing electron-donating or electron-withdrawing groups attached to the benzene ring with 1,2,4-trimethoxybenzene produce (1-alkyl-1-aryl)methylphenyl or tolylsulfones in excellent yield (entries 5–13). The reactions of aralkyl, cyclic and acyclic aliphatic α-amido sulfones with 1,2,4-trimethoxybenzene give the corresponding (1-alkyl-1-aryl)methyl tolylsulfones in 85%, 81%, and 79%, respectively (entries 14–16).

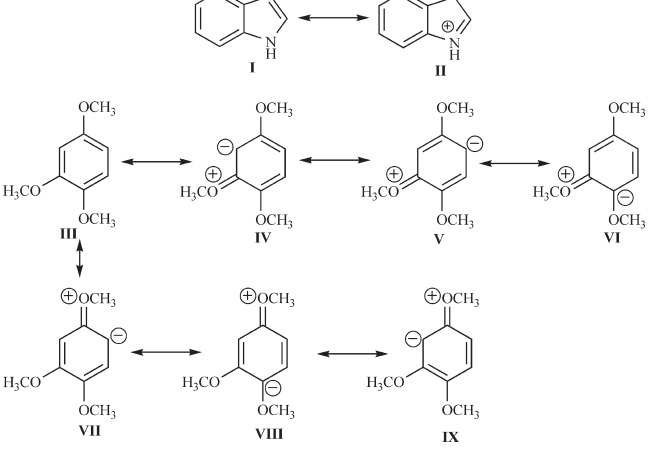
Table 4 shows the Friedel–Crafts alkylation reaction of diaryl sulfones with nucleophilic arene partners. Both heteroaromatic and electron-rich aromatic compounds prove to be very effective to afford the Friedel–Crafts substitution products in good yield as a single regioisomer. The reactions of diaryl sulfones **21** with heteroaromatic indole **22** give corresponding unsymmetrical triaryl methane in 68%, 61%, and 63% yield, respectively (entries 1–3). Similarly, unsubstituted, methoxy- and chloro-substituted diaryl sulfones were also reacted smoothly with 1,2,4-trimethoxybenzene to afford the corresponding bis-symmetrical triaryl methanes in good yield (entries 5–8). The reactions of *o*- and *p*-chloro diarylsufones with 1,2,4-trimethoxybenzene gave corresponding products in 56% and 64% yield, respectively (entries 7 and 8).The *o*-chloro isomer shows less yield, which might be due to the steric and electronic effects of the chlorine substituent (entry 7).

We propose a plausible mechanism that could explain the formation of compounds **23** in the following manner (Figure 3). $InBr_3$ catalyzes the formation of *N*-acyliminium ion **12** by elimination of arenesulfinic acid ($ArSO_2H$) from the α-amido sulfones **10**. Reaction of the strong electrophiles **12** with electron-rich arene **17** gives the Fredel–Crafts products **24**. The elimination of carbamate from **24** by $InBr_3$ may lead to formation of oxonium ions **25**. The oxonium ions **25** can react with arenesulfinic acid ($ArSO_2H$) to produce the diaryl sulfones **18**. The diaryl sulfones **18** in presence of $InBr_3$ result in the second oxonium ions **26** that react with indole **8** in a second Fredel–Crafts reaction to afford triaryl methanes **23**.[26,27]

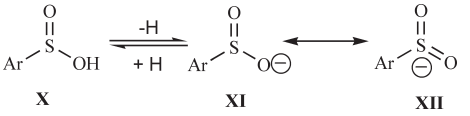
Conclusion

In conclusion, we have demonstrated $InBr_3$-catalyzed Friedel–Crafts alkylations of heteroaromatic or electron-rich aromatic compounds with α-amido sulfones. The catalyst system also allows a controlled double electrophilic aromatic substitution that provides access to unsymmetrical and bis-symmetrical triaryl methanes with wide structural diversity. α-Amido sulfones are employed for the first time in the synthesis of the unsymmetrical and bis-symmetrical triaryl methanes. Further investigation of the reaction under other reaction conditions is currently in progress.

(26) The electron-rich arene (e.g., indole or 1,2,4-trimethoxybenzene) having various resonance structures (**I** to **X**). The active resonance structures are **II**, **V**, and **VII** for the addition reaction.



The deprotonation of arenesulfinic acid (**X**) leads to the formation of sulfinate ion. This shows two resonance structures, *O*-sulfinate (**XI**) and *S*-sulfinate (**XII**). The *S*-sulfinate (**XII**) could be more nucleophilic than *O*-sulfinate (**XI**).



In the synthesis of triaryl methanes, the addition of carbanion (**II** or **V**) derived from electron-rich arene is more favorable than *S*-sulfinate (**XII**) from arenesulfinic acid. This may be due to the higher nucleophilicity of the **II** or **V**.

(27) Kice, J. C.; Large, G. B. *J. Am. Chem. Soc.* **1968**, *90*, 4069.

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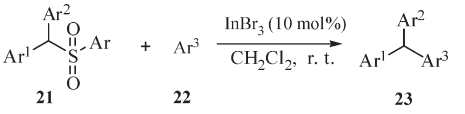
TABLE 4. Synthesis of Triaryl Methanes from Diaryl Methylsulfones[a,b]



Ar = Ph, 4-MePh Ar^1 = Aryl
$Ar^2 = Ar^3$ = Electron-rich aromatic or heteroaromatic indole compounds

	diaryl sulfone **21**					
entry	Ar	Ar^1	Ar^2	Ar^3 **22**	product **23**	isolated yields (%)[c]
1	Ph	4-MeOPh	1,2,4-$(OCH_3)_3C_6H_3$	indole	**23a**	68
2	4-MePh	4-MeOPh	1,2,4-$(OCH_3)_3C_6H_3$	indole	**23a**	61
3	4-MePh	4-MeOPh	indole	1,2,4-$(OCH_3)_3C_6H_3$	**23a**	63
4	Ph	Ph	1,2,4-$(OCH_3)_3C_6H_3$	1,2,4-$(OCH_3)_3C_6H_3$	**23b**	65
5	4-MePh	Ph	1,2,4-$(OCH_3)_3C_6H_3$	1,2,4-$(OCH_3)_3C_6H_3$	**23b**	59
6	4-MePh	4-MeOPh	1,2,4-$(OCH_3)_3C_6H_3$	1,2,4-$(OCH_3)_3C_6H_3$	**23c**	67
7	4-MePh	2-ClPh	1,2,4-$(OCH_3)_3C_6H_3$	1,2,4-$(OCH_3)_3C_6H_3$	**23d**	56[d]
8	4-MePh	4-ClPh	1,2,4-$(OCH_3)_3C_6H_3$	1,2,4-$(OCH_3)_3C_6H_3$	**23e**	64

[a]Reaction conditions: diaryl sulfone (1.0 mmol), heteroaromatic indole or electron-rich aromatic compound (1.1 mmol), $InBr_3$ (0.1 mmol), and CH_2Cl_2 (2.0 mL) at r.t. [b]Reaction time is 6.0 h. [c]Yield of isolated product after flash column chromatography. [d]Isolated yield after 7.0 h of reaction time.

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Publication Date (Web): September 21, 2009 | doi: 10.1021/jo9014613

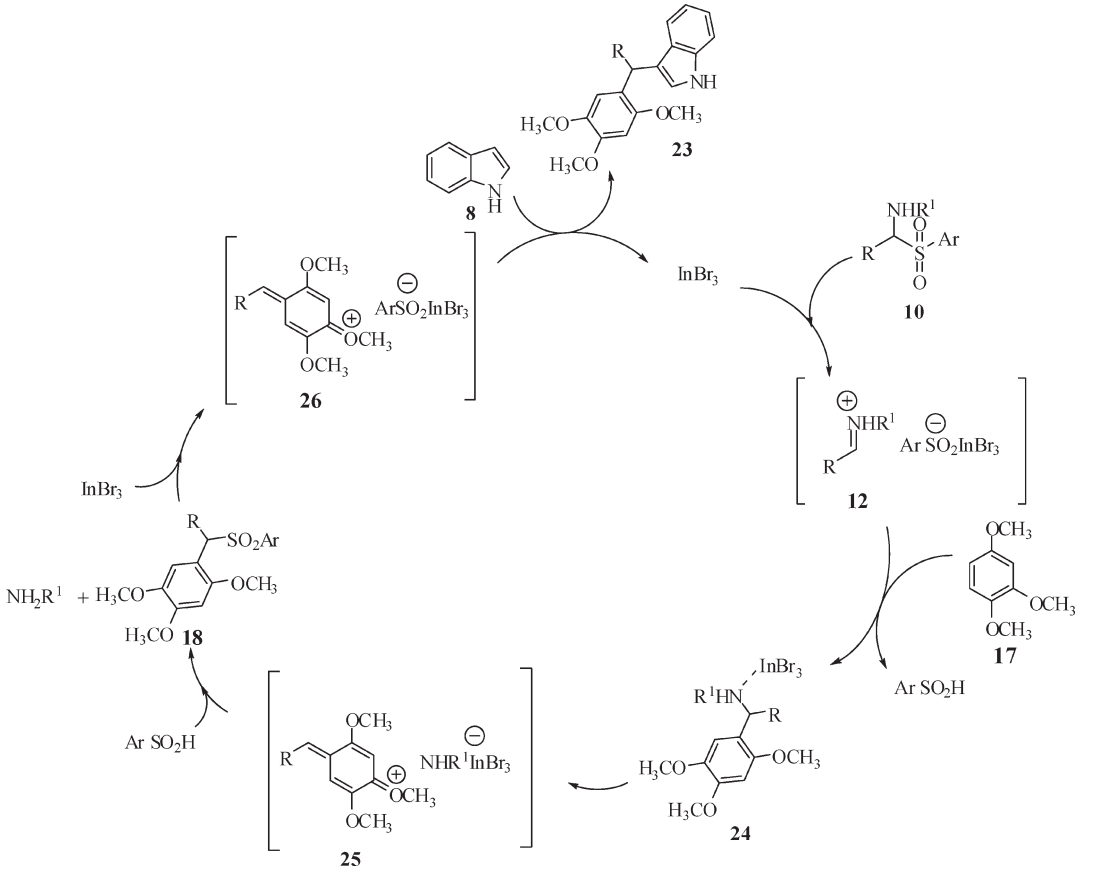

FIGURE 3. Plausible mechanism of $InBr_3$-catalyzed Friedel–Crafts alkylation of α-amido sulfone with electron-rich aromatic compounds and synthesis of triarylmethanes.

Experimental Section

A. Experimental Procedure for the Friedal–Crafts Alkylation of Heteroaroamtic or Electron-Rich Aromatic Compounds. $InBr_3$ (10 mol %) was added to a solution of α-amido sulfones (1 mmol) and heteroaroamtic indoles or electron-rich aromatic compounds in CH_2Cl_2 (2 mL) under nitrogen. The mixture was stirred at r.t. and the reaction was monitored by TLC. After completion, the reaction was quenched with distilled water (5 mL) and the mixture was extracted with EtOAc (5 mL). The combined organic portions were washed with water (5 mL) and saturated aqueous NH_4Cl (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was subjected to flash column chromatography (silica gel, hexane–EtOAc, 4:1 to 3:1) to obtain the pure product.

11a: brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 6.5 Hz, 1H), 7.56 (s, 1H), 7.50−7.40 (m, 5H), 7.23−7.19 (m, 4H), 7.06−6.99 (m, 4H), 5.68 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.3, 135.4, 135.1, 133.4, 130.0, 129.2, 129.1, 128.8, 128.3, 126.9, 124.9, 122.2, 119.8, 118.1, 111.5, 106.8, 69.0, 21.4.[7]

18a: white solid, mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.36−7.33 (m, 3H), 7.19 (d, J = 7.2 Hz, 2H), 6.62 (d, J = 7.5 Hz, 1H), 6.32 (s, 1H), 6.03 (s, 1H), 3.82 (s, 3H), 3.54 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.9, 157.9, 144.1, 136.0, 133.7, 130.8, 130.2, 129.0, 128.5 128.2, 114.3, 104.7, 98.3, 66.4, 55.4, 55.3, 21.6; HRMS-EI (m/z) $[M]^+$ calcd for $C_{22}H_{22}O_4S$ 382.1239, found 382.1263.

B. Experimental Procedure for the Synthesis of Triaryl Methanes. To a mixture of diaryl sulfone (1 mmol) and heteroaromatic indole or electron-rich aromatic compound (1.1 mmol) in CH_2Cl_2 (2 mL) under nitrogen, $InBr_3$ (10 mol %) was added and stirred for 6.0 h at r.t. The progress of the reaction mixture was monitored by TLC. After completion of the reaction, the mixture was quenched with distilled water (5 mL) and then extracted with EtOAc (5 mL). The combined organic portions were washed with water (5 mL) and saturated aqueous NH_4Cl (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was subjected to flash column chromatography (silica gel, hexane−EtOAc, 4:1 to 3:1) to obtain the pure product.

23a: white solid, mp 179−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 7.6 Hz, 3H), 6.99 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 7.2 Hz, 2H), 6.61 (s, 1H), 6.58 (d, J = 7.6 Hz, 1H), 5.98 (s, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.7, 151.2, 147.9, 142.9, 136.8, 136.4, 129.7, 127.1, 124.7, 123.8, 121.9, 120.2, 120.1, 119.2, 114.3, 113.4, 111.0, 98.2, 57.0, 56.6, 56.1, 55.2, 40.0; HRMS-EI (m/z) $[M]^+$ calcd for $C_{25}H_{25}NO_4$ 403.1784, found 403.1786.

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Supporting Information Available: Experimental procedure and characterization data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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