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Brönsted acid-catalyzed synthesis of diarylmethanes under non-genotoxic conditions

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ABSTRACT

Triflic acid and triflimide were found to efficiently catalyze the formation of a wide diversity of diarylmethanes from the non-genotoxic benzylic acetates and electron-rich arenes or heteroarenes. The reaction worked best with acetates capable of generating a stabilized benzylic cationic species. In most cases, the reactions were conveniently run in the absence of solvent under mild conditions.

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The benzylation of arenes is an important reaction for the construction of diarylmethanes, which are found in a substantial number of biologically active compounds and are useful synthetic intermediates. Many groups have reported useful and reliable metal-catalyzed Friedel-Crafts alkylation of aromatic compounds for the construction of diarylmethane derivatives. Syntheses of diarylmethanes based on organozinc¹ or organoboron² derivatives catalyzed by Pd have also been reported. The traditional Friedel-Crafts reaction of arenes has many drawbacks, such as the requirement of fairly drastic conditions incompatible with many functional groups, the generation of large amounts of undesirable by-products or the use of genotoxic benzylating agents (e.g., benzyl chlorides or bromides).³ The increasing concern about health and environmental protection has stimulated the search of new procedures for the synthesis of diarylmethanes. In this context benzylations of arenes using the cheap, non-genotoxic but less electrophilic benzyl alcohols or esters have attracted the attention of several research groups. Several heavy metal-derived catalysts⁴ and in particular rare earth triflates⁵ have been successfully used but these methods often require more complex work-up procedures to remove residues of heavy metals. Recently, Beller and co-workers⁶ showed that iron catalysts efficiently catalyze the arylation of benzyl alcohols and benzyl carboxylates under mild conditions. An important fea-

Table 1

Benzylation and p-methoxybenzylation of anisole



^a Yields determined by ¹H NMR.





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ture of this process was the tolerance of a wide variety of functional groups.

In this context, the observation by Sun and Wang⁷ that molecular iodine efficiently catalyzed the benzylation of arenes with benzyl alcohols is also of particular interest. A last approach which will probably appeal to industrial chemists involves the use of solid heterogeneous Brönstedt and Lewis acid catalysts.⁸

In 1997 we,⁹ and Mikami's group¹⁰ independently introduced trialkylsilyl triflimides as a new class of non-metallic Lewis acid

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Reaction of arenes with benzyl acetates 1a-d

catalysts. These silvlating agents are stronger Lewis acids than the corresponding triflates and catalyze a variety of reactions involving Lewis acid activated carbonyl derivatives.¹² More recently, Martin and co-workers reported an elegant approach to an array of substituted β -heteroaryl propionates by coupling silyl ketene acetals and other π -nucleophiles with alcohols and acetates derived from electron-rich heterocycles in the presence of trimethylsilyl trifluoromethanesulfonate.¹³ However, with less activated benzyl acetates, trialkylsilyl triflimides were again found to be largely superior to the corresponding triflates.¹² In their seminal report, Mikami and co-workers¹⁰ had claimed that TMS-ethers derived from benzyl alcohols could alkylate anisole in the presence of catalytic amounts of TMSNTf₂. However, in these reactions, 1 equiv of HNTf₂ is produced as a result of the aromatization of the tetrahedral intermediate. It was, therefore, not excluded that HNTf₂ could take part in the catalytic process.¹¹ This was debatable in as much as Beller and co-workers⁶ had reported that HCl, HOAc and *p*-toluenesulfonic acid did not catalyze the reaction of *o*-xylene with 1-phenylethylacetate while Lachter and co-workers¹⁴ and more recently Sarca and Laali¹⁵ reported the successful benzylation of arenes promoted by amberlyst 15, niobic acid, or triflic acid in ionic solvents.

Entry	Electrophile	Nucleophile	Main product	<i>T</i> (°C)	t	Cat.	Solvent	Yield ^{a,b} (%)
1	MeO OAc	OH	МеО ОН	rt	20 min	HOTf	No	95
2		OMe	MeO	rt	20 min	HOTf	No	98
3		OMe OMe	MeO OMe	rt	1 h	HOTf	No	90
4		Me	decomposition	rt	20 min	HOTf	No	0
5	OAc 1b	OH	OH (3:2)	100	1 h	HOTf	No	99
6		OMe	OMe (3:2)	100	1 h	HOTf	No	91
7		OMe OMe	OMe OMe (3:1)	100	1 h	HOTf	No	86
8		Me	Me	100	1 h	HOTf	No	89
9	F OAc 1c	OMe	F OMe (3:2)	100	1 h	HOTf	No	71
10	MeO OAc MeO 1d	OMe	MeO MeO OMe	rt	20 min	HOTf	No	81

^a Only the major isomer is shown. When two isomers are formed, ratios are indicated in brackets.

^b Yields were determined by GLC.

We, therefore, decided to test representative Brönsted acids as catalysts of the reaction of anisole with anisyl and benzyl acetates 1 and 2 (Table 1). No solvent was used except with HNTf₂, which was introduced in the reaction mixture as a 0.5 M solution in dichloromethane and HCl as a 4 M solution in dioxane. Reactions were monitored by ¹H NMR.

Phosphoric acid and trifluoroacetic acid did not catalyze the *p*-methoxybenzylation of anisole (entries 1 and 2). HCl gave a poor yield of substitution product at room temperature or at 100 °C for 1 hr. Both triflic acid and triflimide proved to be excellent catalysts in both test reactions (entries 4, 5, 8, and 9). Sulfuric acid efficiently catalyzed the *p*-methoxybenzylation reaction (entry 6) but was inefficient with the less reactive benzylacetate. Methane-sulfonic acid exhibited a moderate catalytic activity as compared to triflic acid and triflimide. The reactions with *p*-methoxybenzyl acetate only gave the *para* isomer. Benzylacetate gave a mixture of *para* and *ortho* substitution products with both HOTf and HNTF₂. The higher reactivity of *p*-methoxybenzyl acetate probably resulted from a faster dissociation of the protonated ester **2** into a cationic species **3** and acetic acid (Scheme 1).

We then examined the scope and limitations of these reactions by varying both the substituent of the acetate and the aromatic nucleophile (Table 2 and 3). HOTf was selected as the standard catalyst (5 mol %).¹⁷ Reactions were run either at room temperature or at 100 °C in a fivefold excess of arene and in most cases, in the absence of solvent.

Electron-rich aromatics, such as phenols or the corresponding ethers gave high yields of benzylation products at room temperature for **1a** (Table 2, entries 1-3) and **1d** (entry 10) and 100 °C

for **1b** (entries 5–7) and **1c** (entry 9). Benzylacetate **1b** also gave an excellent yield of the substitution product with *p*-xylene (entry 8) in contrast with anisylacetate **1a**, which only yielded decomposition products (entry 4). This should probably be assigned to a competitive reaction of the cationic species **3** with the more nucleophilic aromatic ring of **1a** (Scheme 1).

Not surprisingly electron-rich aromatics, such as furan (Table 3, entries 1 and 2), *N*-phenylsulfonyl pyrrole (entry 3), indole (entry 4) and *N*-phenylsulfonyl indole (entry 5) also reacted with anisylacetate at room temperature in the presence of 5 mol % HOTf catalyst The reaction with furan required dilution with dichloromethane to avoid the decomposition of furan in these very acidic conditions.

Indole could not be used with the less reactive benzyl acetate: it consumed the acid catalyst and led to some decomposition product and unreacted indole as shown by ¹H NMR (entry 9). The less nucleophilic *N*-phenylsulfonyl indole yielded only the 3-substitution products (entries 5 and 10). Furan also reacted regioselectively to exclusively yield the 2-substitution product. However, phenyl-sulfonyl pyrrole gave a mixture of 2- and 3-substituted products with **1b** (entry 8) probably as a result of a higher reaction temperature and the steric protection of the 2-position by the large substituent on nitrogen.

The flexibility and versatility of this synthesis of diarylmethanes were further illustrated by the reaction of arenes and heteroarenes with acetates **1e–g** (Table 4). Disappointingly our attempts to react the thiophene-derived acetate **1e** with anisole in the presence of triflic acid only led to untractable mixtures (entry 1). We felt that this probably resulted from the unstability of **1e** in these strongly

T (°)C Cat. Entry Electrophile Nucleophile Product t Solvent Yield (%) 1 No 0 `OAc 2 CH_2Cl_2 72 HOTF rt 10 min MeO 1a SO₂Ph 3 HOTF 98 5 min No rt 100 HOTf 4 1 h No 60 5 rt 10 min HOTf No 95 ŚO₂Ph ŚO₂Ph 6 HOTF CH_2Cl_2 0 OAc 7 Decomposition rt 20 min HNTf₂ CH_2Cl_2 0 1b SO₂Ph SO₂Ph 8 100 1 h HOTf No 79 (3:2) ·SO₂Ph 100 1 h HOTf 0 9 No reaction No 100 HOTf 10 1 h No 88 ŚO₂Ph ŚO₂Ph

Reactions of electron-rich heteroarenes with benzyl- and anisyl acetates

Table 4

Reactions of arenes and heteroarenes with heteroaryl methylacetates



^a All reactions were run in dichloromethane at room temperature.

^b Yields determined by after 20 min.

acidic conditions and that a weaker acid should be used. Rewardingly the substitution product was obtained in 98% yield in the presence of 5 mol % of HNTf₂ (entry 2).^{16,18} These conditions allowed also to couple **1e** to the highly acid-sensitive furan. Both reactions were regioselective. Triflimide was also an efficient catalyst of the reaction of anisole or furan with furan and pyrrolederived acetates **1f** and **1g**.

All these reactions are believed to involve the formation of a cationic species resulting from the dissociation of the protonated acetate (Scheme 1). The nature of this cationic intermediate (planar cation or pyramidal ion pair) should influence the stereochemical course of a reaction involving one enantiomer of an acetate reagent derived from a secondary benzyl alcohol. We, therefore, decided to study the stereochemical course of the reaction of anisole with (*s*)-benzylmethyl acetate **1h** in the presence of 5 mol % HOTf (Scheme 2). After 30 min. at 100 °C, a 3:2 mixture of racemic (HPLC) *para*- and *ortho*-benzylation products were obtained. This confirmed the formation of a planar cationic intermediate.

We believe that this synthetic procedure should appeal to the synthetic chemists: (a) it involves stable, easily handled and nongenotoxic benzylating agents, (b) it avoids the use of metal catalysts, (c) in most cases a solvent is not necessary, (d) it does not require protection from air or moisture, (e) it is operationally simple





and economical, (f) yields are high, (g) the scope is fairly broad and (h) it is environmentally friendly.

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- 17. General procedure for the alkylation reaction of anisole with anisyl acetate in the presence of triflic acid: 430 μL of anisyl acetate (2.5 mmol, 1 equiv) and 2.2 mL

of anisole (12.25 mmol, 5 equiv) were placed into a 10 mL round-bottom flask equipped with a magnetic stir-bar. Then 11 μ L 5% of pure triflic acid (0.125 mmol) was added and the solution was stirred for 20 min. The crude was analyzed by ¹H NMR and GC–MS. Purification by column chromatography gave 484 mg (85% yield) of bis(4-methoxyphenyl)methane, which was identical to an authentic sample.

18. General procedure for the alkylation reaction of anisole with thiophenyl methyl acetate in the presence of triflimide: 330 µL of (thiophen-2-yl)methyl acetate (2.5 mmol, 1 equiv) and 2.2 mL of anisole (12.25 mmol, 5 equiv) were placed into a 10 mL round-bottomed flask equipped with a magnetic stir-bar. After

addition of 250 µL of a 0.5 M solution of HNTf₂ in CH₂Cl₂, the solution was stirred for 20 min at room temperature. The crude mixture was analyzed by NMR and GC–MS. Purification by column chromatography gave 408 mg (80% yield) of 2-(4-methoxybenzyl)thiophene, which was identified by ¹H, ¹³C, and HRMS. ¹H NMR (300 MHz, CDCl₃): δ = 7.20 (d, *J* = 8.9 Hz, 2H), 7.17 (dd, *J* = 1.3, 5.1 Hz, 1H), 6.95 (dd, *J* = 3.4, 5.3 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.82 (dd, *J* = 1.1, 3.4 Hz, 1H), 4.14 (s, 2H), 3.83 (s, 3H); ¹³C NMR (300 MHz, CDCl₃): δ = 158.3, 144.8, 132.6, 129.6, 126.8, 124.9, 123.8, 113.9, 55.3, 35.2. HRMS calcd for C₁₂H₁₂OSAg: 310.9654 (M+Ag⁺), found: 310.9655.