

# Iron-Catalyzed Benzylation Reaction of Arenes with Benzyl Thiocyanates

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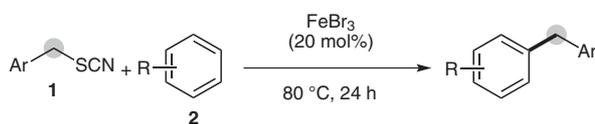
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**Abstract:** A novel, regioselective protocol for the synthesis of diphenylmethane derivatives has been developed by using iron-catalyzed Friedel–Crafts reaction of arenes with benzyl thiocyanates. In the presence of FeBr<sub>3</sub>, a variety of benzyl thiocyanates underwent the reaction with arenes to selectively afford the corresponding diarylmethane derivatives in moderate to high yields.

**Key words:** iron, benzylation, Friedel–Crafts reaction, benzyl thiocyanate, diarylmethane

The diarylmethane moiety is a valuable structural unit in numerous biological compounds.<sup>1</sup> For this reason, considerable effort has been devoted to the synthesis of diarylmethane derivatives.<sup>2–8</sup> Among the developed approaches, the Friedel–Crafts reaction is one of the most efficient methods for the formation of diarylmethane derivatives.<sup>2</sup> Although the Friedel–Crafts method can provide efficient access to substituted diarylmethane derivatives, there are noticeable drawbacks associated with this approach; it usually requires stoichiometric amounts of Lewis acids, high temperatures, and/or a large excess of arene for the relatively low nucleophilic aromatic compounds.<sup>3–5</sup> To overcome these limitations, palladium- or ruthenium-catalyzed C–H bond activation strategies for direct benzylation of aromatic compounds were developed recently.<sup>6</sup> However, both palladium and ruthenium catalysts are highly expensive. Thus, development of some new protocols using inexpensive and more environmentally benign catalysts is interesting. Here, we wish to report a novel Friedel–Crafts-type reaction for direct benzylation of arenes with benzyl thiocyanate catalyzed by inexpensive iron salts (Scheme 1). To the best of our knowledge, this is the first example of direct benzylation of aromatic compounds with benzyl thiocyanate using a catalytic amount of iron salts.



**Scheme 1** Fe-catalyzed benzylation reaction

The reaction between (thiocyanatomethyl)benzene (**1a**) and *p*-xylene (**2a**) was investigated to optimize the reaction conditions; the results are summarized in Table 1. Initially, three iron salts, FeCl<sub>3</sub>, FeBr<sub>3</sub> and FeF<sub>3</sub>, were examined (Table 1, entries 1–3). Both FeCl<sub>3</sub> and FeBr<sub>3</sub> were suitable catalysts for the reaction, affording the target product **3** in 25% and 29% yields, respectively (Table 1, entries 1 and 2). However, FeF<sub>3</sub> had no effect on this reaction (Table 1, entry 3). Further screening revealed that the amount of FeBr<sub>3</sub> did not affect the reaction significantly (Table 1, entries 4 and 5). Upon studying the effect of reaction temperature, it turned out that the reaction performed at 80 °C gave the best results (Table 1, entries 2 and 6–8). In light of these results, a number of other solvents, including *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), toluene and MeCN, were tested, but they were not suitable for this reaction (Table 1, entries 9–12). We were pleased to find that the amount of *p*-xylene (**2a**) affected the yield of **3**: the yield was enhanced sharply to 63% when four equivalents *p*-xylene (**2a**) was added (Table 1, entry 13), and to 75% at 10 equivalents *p*-xylene (**2a**; Table 1, entry 14). Notably, in the presence of 20 equivalents *p*-xylene (**2a**) the target product **3** was obtained in 85% yield under solvent-free conditions (Table 1, entry 15). The results demonstrated that, in the presence of 2,6-di-*tert*-butylpyridine or NaHCO<sub>3</sub>, the reaction did not take place, and substrate **1a** was almost completely recovered (Table 1, entries 16 and 17).

With the optimal conditions in hand, the reaction scope was explored (Table 2). In the presence of FeBr<sub>3</sub>, a variety of (thiocyanatomethyl)benzenes **1b–h** were first examined by reacting with *p*-xylene (**2a**; Table 2, entries 1–7). The results demonstrated that several substituents, including Me, MeO, F and Br, on the aromatic ring of (thiocyanatomethyl)benzenes were well-tolerated (Table 2, entries 1–6). Substrate **1c**, with an *ortho*-methyl group, for instance, was treated with *p*-xylene (**2a**) and FeBr<sub>3</sub> to afford the desired product **5** in good yield (Table 2, entry 2). A 23% yield was still isolated from methoxy-substituted substrate **1e** (Table 2, entry 4). Interestingly, substrates **1f** and **1g**, with a fluorine or bromine group, were compatible with the optimal conditions (Table 2, entries 5 and 6). For example, treatment of substrate **1g** (with a Br group) with *p*-xylene (**2a**) and FeBr<sub>3</sub> furnished the corresponding product **9** in 67% yield (Table 2, entry 6). Gratifyingly, 3-(thiocyanatomethyl)thiophene (**1h**), a heterocyclic compound, was also suitable for the reaction (Table 2, entry

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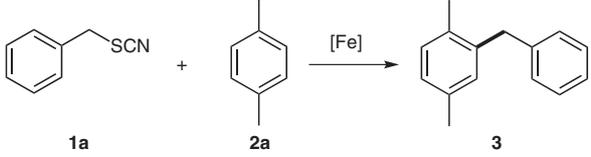
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7). Subsequently, a range of arenes **2** were investigated under the optimal conditions (Table 2, entries 8–14). The results showed that electron-rich arenes were compatible with the optimal conditions. Notably, several substituents, such as Me, MeO, Cl or OH, on the aryl ring in substrates **2** were perfectly tolerated. 1-Chloro-4-methoxybenzene (**2e**), for instance, selectively reacted with (thiocyanatomethyl)benzene (**1a**) and FeBr<sub>3</sub> to give the desired product **15** in 89% yield (Table 2, entry 11). It was noted that substrates **2d**, **2f** and **2g** gave a mixture of *para*- and *ortho*-products in moderate yields (Table 2, entries 10, 12 and 13). Phenol (**2h**) was also a suitable substrate for the

**Table 1** Screening Optimal Conditions<sup>a</sup>



Entry	[Fe] (mol%)	Solvent	Temp (°C)	Yield (%) <sup>b</sup>
1	FeCl <sub>3</sub> (20)	DCE	120	25
2	FeBr <sub>3</sub> (20)	DCE	120	29
3	FeF <sub>3</sub> (20)	DCE	120	trace
4	FeBr <sub>3</sub> (50)	DCE	120	27
5	FeBr <sub>3</sub> (100)	DCE	120	34
6	FeBr <sub>3</sub> (20)	DCE	100	32
7	FeBr <sub>3</sub> (20)	DCE	80	31
8	FeBr <sub>3</sub> (20)	DCE	60	15
9	FeBr <sub>3</sub> (20)	DMF	80	trace
10	FeBr <sub>3</sub> (20)	THF	80	trace
11	FeBr <sub>3</sub> (20)	toluene	80	trace
12	FeBr <sub>3</sub> (20)	MeCN	80	trace
13 <sup>c</sup>	FeBr <sub>3</sub> (20)	DCE	80	63
14 <sup>d</sup>	FeBr <sub>3</sub> (20)	DCE	80	75
15 <sup>e</sup>	FeBr <sub>3</sub> (20)	neat	80	85
16 <sup>e f</sup>	FeBr <sub>3</sub> (20)	neat	80	0
17 <sup>e g</sup>	FeBr <sub>3</sub> (20)	neat	80	0

<sup>a</sup> Reagents and conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), [Fe] and solvent (3 mL), 24 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> **2a** (4 equiv).

<sup>d</sup> **2a** (10 equiv).

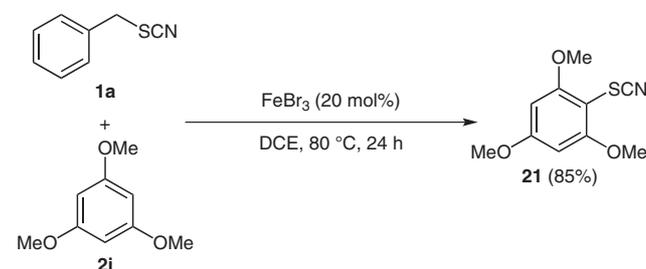
<sup>e</sup> **2a** (20 equiv).

<sup>f</sup> 2,6-di-*tert*-butylpyridine (2 equiv) was added.

<sup>g</sup> NaHCO<sub>3</sub> (2 equiv) was added.

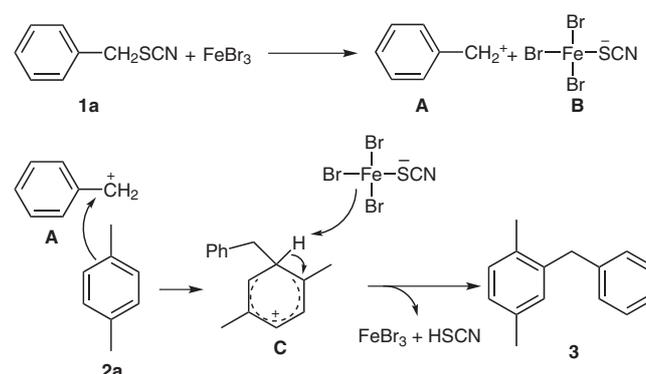
reaction with **1a**, selectively giving the *para*-substituted benzylation product **20** in 55% yield (Table 2, entry 14). However, electron-deficient nitrobenzene did not undergo the reaction (Table 2, entry 15).

Surprisingly, the reaction of 1,3,5-trimethoxybenzene (**2i**) with (thiocyanatomethyl)benzene (**1a**) and FeBr<sub>3</sub> afforded a thiocyanation product **21** in 85% yield, and not the desired diarylmethane (Scheme 2).<sup>9</sup>



**Scheme 2** FeBr<sub>3</sub>-catalyzed reaction of 1,3,5-trimethoxybenzene (**2i**) with (thiocyanatomethyl)benzene (**1a**)

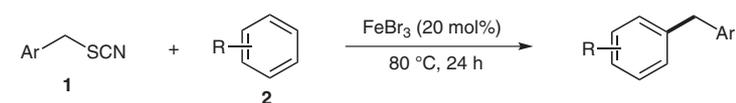
A possible mechanism, outlined in Scheme 3, was proposed.<sup>2,3</sup> Initially, the reaction of **1a** with FeBr<sub>3</sub> affords a cation intermediate **A** and an anion intermediate **B**. Intermediate **A** subsequently undergoes electrophilic alkylation with substrate **2a** to form intermediate **C**. Finally, deprotonation of intermediate **C** gives the target product **3**.

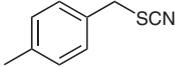
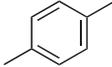
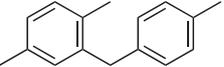
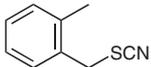
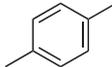
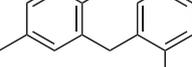
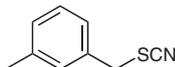
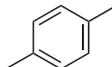
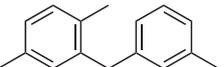
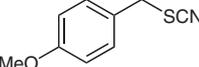
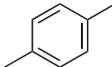
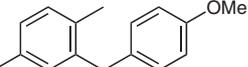
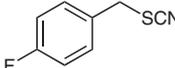
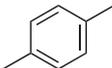
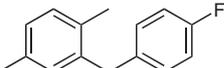
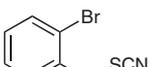
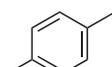
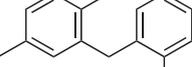
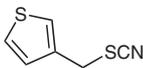
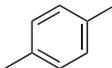
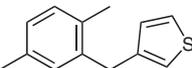
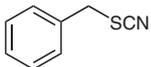
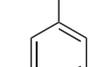
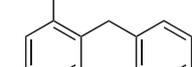
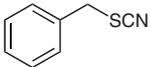
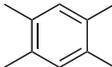
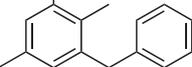
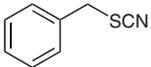
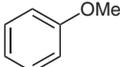
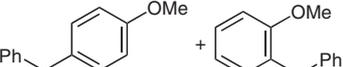
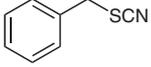
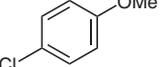
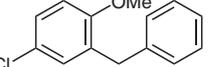


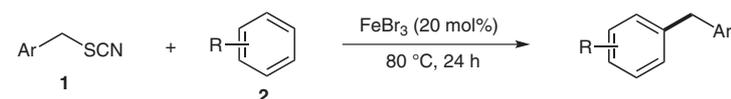
**Scheme 3** Possible mechanism

In summary, we have developed a novel protocol for the synthesis of diarylmethanes using inexpensive and environmentally benign iron catalysts.<sup>10</sup> This method allows direct benzylation of aromatic compounds with numerous thiocyanates with high regioselectivity under neat conditions.

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

**Table 2** Synthesis of Diarylmethanes by Fe-Catalyzed Friedel–Crafts-Type Reaction<sup>a</sup>

Entry	Compound 1	Compound 2	Product	Isolated yield (%)
1	 <b>1b</b>	 <b>2a</b>	 <b>4</b>	71
2	 <b>1c</b>	 <b>2a</b>	 <b>5</b>	73
3	 <b>1d</b>	 <b>2a</b>	 <b>6</b>	77
4	 <b>1e</b>	 <b>2a</b>	 <b>7</b>	23
5	 <b>1f</b>	 <b>2a</b>	 <b>8</b>	81
6	 <b>1g</b>	 <b>2a</b>	 <b>9</b>	67
7	 <b>1h</b>	 <b>2a</b>	 <b>10</b>	35
8	 <b>1a</b>	 <b>2b</b>	 <b>11</b>	75
9 <sup>b</sup>	 <b>1a</b>	 <b>2c</b>	 <b>12</b>	95
10 <sup>b</sup>	 <b>1a</b>	 <b>2d</b>	 <b>13/14</b> (10:1) <sup>c</sup>	70
11 <sup>b</sup>	 <b>1a</b>	 <b>2e</b>	 <b>15</b>	89

**Table 2** Synthesis of Diarylmethanes by Fe-Catalyzed Friedel–Crafts-Type Reaction<sup>a</sup> (continued)

Entry	Compound 1	Compound 2	Product	Isolated yield (%)
12				36
	<b>1a</b>	<b>2f</b>	<b>16/17</b> (1.6:1) <sup>c</sup>	
13				35
	<b>1a</b>	<b>2g</b>	<b>18/19</b> (1.8:1) <sup>c</sup>	
14 <sup>b</sup>				55
	<b>1a</b>	<b>2h</b>	<b>20</b>	
15 <sup>b</sup>			–	0
	<b>1a</b>	<b>2i</b>		

<sup>a</sup> Reagents and conditions: **1** (0.4 mmol), **2** (20 equiv), FeBr<sub>3</sub> (20 mol%), 80 °C, 24 h.

<sup>b</sup> **1** (0.4 mmol), **2** (10 equiv) in DCE (3 mL) for 24 h.

<sup>c</sup> The products were determined by <sup>1</sup>H NMR analysis.

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- (10) **Typical Procedure:** A mixture of benzyl thiocyanate (**1a**; 0.4 mmol), substrate (**2a**; 20 equiv), and FeBr<sub>3</sub> (23.4 mg, 20 mol%) was stirred in a Schlenk tube at 80 °C (oil bath temperature) until complete consumption of starting material was observed (reaction monitored by TLC and GC-MS analyses). The mixture was filtered through a crude column, washed with ethyl acetate, and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the product **3**.

**Benzyl-1,4-dimethylbenzene (3):** Yellow oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.25 (t, *J* = 7.5 Hz, 2 H), 7.19–7.15 (m, 1 H), 7.11 (d, *J* = 7.5 Hz, 2 H), 7.04 (d, *J* = 7.6 Hz, 1 H), 6.95 (d, *J* = 7.7 Hz, 1 H), 6.92 (s, 1 H), 3.94 (s, 2 H), 2.28 (s, 3 H), 2.18 (s, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 140.5, 138.7, 135.3, 133.4, 130.8, 130.2, 128.7, 128.3, 127.1, 125.8, 39.4, 21.0, 19.2; MS (EI, 70 eV): *m/z* (%) = 196 (90) [M]<sup>+</sup>, 181 (100), 118 (43).

**Typical Procedure:** A mixture of benzyl thiocyanate (**1a**; 0.4 mmol), 1,3,5-trimethoxybenzene (**2i**; 10 equiv), FeBr<sub>3</sub> (23.4 mg, 20 mol%) and DCE (3 mL) was stirred in a Schlenk tube at 80 °C (oil bath temperature) until complete consumption of starting material was observed (reaction monitored by TLC and GC-MS analyses). The mixture was filtered through a crude column, washed with ethyl acetate, and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the product **21**.

**1,3,5-Trimethoxy-2-thiocyanatobenzene (21):** Yellow soild; mp 159.3–160.5 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 6.15 (s, 2 H), 3.92 (s, 6 H), 3.84 (s, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 164.2, 161.3, 111.8, 91.3, 89.7, 56.3, 55.6; LRMS (EI, 70 eV): *m/z* (%) = 225 (100) [M]<sup>+</sup>, 179 (34).

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