Iron(III) Chloride Catalyzed Formation of Aryl Hydrazides from Electron-Rich Arenes and Azodicarboxylates

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Abstract: Iron(III) chloride-catalyzed direct amination of electron-rich arenes with azodicarboxylates gives the corresponding aryl hydrazides in moderate to good yields within two minutes under mild conditions. This method will serve as an important tool for the synthesis of bioactive nitrogen-containing products and pharmaceuticals.

Key words: catalysis, iron, aminations, arenes, hydrazides

Functionalized aryl hydrazides and their derivatives are useful intermediates for the synthesis of nitrogen-containing heterocycles and bioactive medicinal and agrochemical compounds.[1] Consequently, a variety of protocols have been developed for synthesizing aryl hydrazides from azodicarboxylates.[1,2] Among these, the conventional protocols involve aminations of aryllithium reagents,[3a,b] aryl Grignard reagents,[3b] or arylzinc halides[3c] with azodicarboxylates. Alternatively, Lewis acids or Brønsted acids can be used as efficient catalysts for reactions of electron-rich arenes with azodicarboxylates.[4] In an important contribution to this field, Zhang and co-workers described the first example of a catalytic direct amination of electron-deficient arenes with azodicarboxylates.[5] However, their modified method used air-sensitive and expensive gold(III) chloride as a catalyst, which detracts from the synthetic appeal of this transformation. Mandal and co-workers recently described a ruthenium chloride-catalyzed direct amination of arenes with azodicarboxylates; this method can be applied to amination of a broad spectrum of arenes, including those with certain electron-withdrawing groups, which give modest to low yields.[4k] Recently, transition metal-catalyzed coupling reactions of arylboronic acids with azodicarboxylates to give aryl-substituted hydrazines have been developed.[6] Although these methods are useful, the development of new methods that do not involve expensive reagents or harsh conditions is desirable to provide an environmentally friendly catalytic system for the direct amination of arenes.

In the last decade, iron salts have attracted the attention of synthetic organic chemists because of their ready availability, environmental friendliness, and low cost, along with their exceptional reactivity.[7] Because of the ease with which they can change their oxidation state and their distinct Lewis acid character, iron catalysts have been used in several protocols for the synthesis of various organic compounds through the formation of carbon−carbon or carbon−heteroatom bonds.[7,8] In a prominent case, iron has been shown to be an efficient catalyst for the alkenylation of simple arenes with aryl-substituted alkynes, giving new C−C bonds from aromatic C–H bonds.[8b]

We recently demonstrated that iron(III) chloride is a highly effective catalyst for Friedel−Crafts reactions of electron-rich arenes with imines or aziridines.[8f] We therefore set out to look for a new transformation using this catalyst system, with the aim of demonstrating its wide range of potential applications. Here, we describe the results from our attempts to develop a new iron(III) chloride catalyzed direct amination of electron-rich arenes with azodicarboxylates under mild conditions.

First, we examined the use of iron(III) chloride (5 mol%) as a catalyst for the reaction of mesitylene (**1a**) with diisopropyl azodicarboxylate (**2a**) in nitromethane at room temperature (Table 1, entry 1). Gratifyingly, this reaction was completed within two minutes, affording the desired product **3a** in 95% yield. A similar yield (91%) was obtained when iron(III) chloride hexahydrate was used as the catalyst instead of the anhydrous salt (entry 2). Other iron salts, such as iron(III) sulfate, iron(III) nitrate nonahydrate, tris(acetylacetonato)iron, or iron(II) sulfate heptahydrate, were ineffective catalysts for the formation of aryl hydrazide **3a** (entries 3–6). Moderate yields of the desired product **3a** were obtained by using iron(II) chloride or iron(II) triflate as the catalyst (entries 7 and 8, respectively). An evaluation of various solvents did not produce any better results (entries 9–11). When aqueous hydrochloric acid (20 mol%) was used as the catalyst, none of the desired product was obtained (entry 12). These results confirm the high catalytic activity of iron(III) chloride.

Next, we examined the substrate scope of the iron-catalyzed direct amination of simple arenes with azodicarboxylates under the optimized reaction conditions (Table 1, entry 1). As shown in Table 2, this method was effective for electron-rich arenes, and the catalyst was highly efficient in this reaction. Almost all reactions of electron-rich arenes were complete within two minutes and gave moderate to excellent isolated yields of the corresponding aryl hydrazides **3**. For example, amination of naphthalene and 1-methoxynaphthalene in the presence of 5 mol% of the

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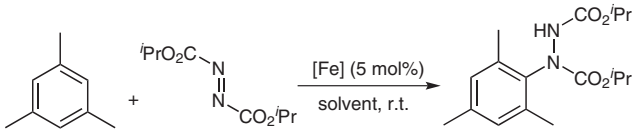
Table 1 Amination of Mesitylene (**1a**) with Diisopropyl Azodicarboxylate (**2a**) in the Presence of Various Iron Salts



1a **2a** **3a**

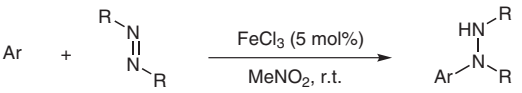
Entry[a]	Catalyst	Solvent	Time	Yield[b] (%)
1	$FeCl_3$	$MeNO_2$	2 min	95
2	$FeCl_3·6H_2O$	$MeNO_2$	2 min	91
3	$Fe_2(SO_4)_3$	$MeNO_2$	2 h	–
4	$Fe(NO_3)_3·9H_2O$	$MeNO_2$	2 h	trace
5	$Fe(acac)_3$	$MeNO_2$	2 h	–
6	$Fe(SO_4)_2·7H_2O$	$MeNO_2$	2 h	trace
7	$FeCl_2$	$MeNO_2$	2 min	89
8	$Fe(OTf)_2$	$MeNO_2$	2 min	77
9	$FeCl_3$	CH_2Cl_2	12 h	26
10	$FeCl_3$	DCE	12 h	35
11	$FeCl_3$	THF	12 h	trace
12	HCl[c]	$MeNO_2$	12 h	–

[a] Reaction conditions: **2a** (0.5 mmol), **1a** (1 mmol), catalyst (5 mol%), solvent (2 mL), r.t.
[b] Isolated yield based on **2a**.
[c] 0.1 mmol catalyst (20 mol%).

iron catalyst gave good yields within two minutes (Table 2, 3f and **3g**). For the reactions of durene and 1,3,5-trimethoxybenzene, yields of the corresponding aryl hydrazides **3b** and **3c** were moderate, even after a prolonged reaction time. This low yield might be the result of steric hindrance on the benzene ring. Gratifyingly, however, the aryl hydrazides **3c** could be isolated in 80% yield by using iron(II) triflate as the catalyst. The reactions of 1,2-dimethoxybenzene with azidocarboxylates **2** were very complex, giving mixtures of the monoaminated products **3e** or **3j** and other unknown products. To our disappointment, electron-deficient arenes such as chlorobenzene, fluorobenzene, or iodobenzene were not good partners for this kind of transformation, even with prolonged reaction times and increased reaction temperatures. Surprisingly, amination of 1-iodo-4-methoxybenzene with **2a** at room temperature for 24 hours gave the desired aryl hydrazide **3h** in an isolated yield of 40%. With regard to the azodicarboxylate reactant, commercially available dibenzyl azodicarboxylate (**2b**) reacted with simple arenes **1** to give the expected products in moderate to good yields (**3i**, 84%; **3j**, 56%). Overall, however, electron-rich arenes are the most reactive substrates for these aminations.

In summary, we have developed a novel and simple direct amination reaction of electron-rich arenes with azodicarboxylates that is catalyzed by iron(III) chloride and provides a convenient route for the synthesis of aryl hydrazides. The protocol has the advantages of providing high efficiency (reaction times of less than 2 minutes), requiring low-price reactants and catalysts, being environmentally benign, and involving simple experimentally operations. This method might therefore serve as an important tool for efficient synthesis of biologically active nitrogen-contained products and pharmaceuticals.

Table 2 Iron(III) Chloride Catalyzed Aminations of Various Arenes **1** with Azodicarboxylates **2**



1 **2a** R = CO_2*i*-Pr; **2b** R = CO_2Bn **3**

Product	Ar	R	Yield (%)
3a	2,4,6-$Me_3C_6H_2$	CO_2*i*-Pr	95
3b	2,3,5,6-Me_4C_6H	CO_2*i*-Pr	70[b]
3c	2,4,6-$(MeO)_3C_6H_2$	CO_2*i*-Pr	68 (80)[c]
3d	2,5-$(MeO)_2C_6H_3$	CO_2*i*-Pr	65
3e	3,4-$(MeO)_2C_6H_3$	CO_2*i*-Pr	56
3f	1-naphthyl	CO_2*i*-Pr	81
3g	4-methoxy-1-naphthyl	CO_2*i*-Pr	87
3h	2-MeO-5-IC_6H_3	CO_2*i*-Pr	40[d]
3i	2,4,6-$Me_3C_6H_2$	CO_2Bn	84
3j	3,4-$(MeO)_2C_6H_3$	CO_2Bn	56

[a] Yields are isolated yields based on the azodicarboxylate **2**.
[b] At r.t. for 30 min.
[c] $Fe(OTf)_2$ catalyst.
[d] At r.t. for 24 h.

NMR spectra were recorded with Agilent 400-MR DD2, 600-MR DD2, and Bruker AV500 spectrometers (400 or 500 MHz for ^1H, 100, 125 or 150 MHz for ^{13}C) with $CDCl_3$ as a solvent at 20−25 °C. High-resolution mass spectra were recorded on a Finnigan MAT8430 Q-TOF MS spectrometer. IR spectra were recorded as liquid films on a Bruker Tensor 27 spectrophotometer. Column chromatography was carried out on silica gel (300−400 mesh), and TLC analyses were performed on silica gel coated plates (HSGF254, Yantai Jiangyou Silica Gel Development Co., Ltd.). All reactions were carried out under argon. All commercial materials were used without further purification.

Diisopropyl 1-Mesitylhydrazine-1,2-dicarboxylate (3a)[5]; Typical Procedure

Azodicarboxylate **2a** (0.5 mmol) was added to a stirred solution of arene **1a** (1 mmol) and $FeCl_3$ (5 mol%) in anhyd $MeNO_2$ (3 mL) at r.t. under argon. When the reaction was complete (TLC, < 2 min), the reaction was quenched with H_2O (10 mL), and the mixture was extracted with EtOAc (2 × 10 mL). Evaporation of the solvent followed by purification of the residue by flash chromatography [silica gel, PE–EtOAc (8:1)] gave a white solid; yield: 153 mg (95%); mp 90.0–91.0 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.87 (s, 2 H), 6.79–6.70 (m, 1 H), 5.02–4.94 (m, 2 H), 2.30–2.26 (m, 9 H), 1.31–1.15 (m, 12 H).

Diisopropyl 1-(2,3,5,6-Tetramethylphenyl)hydrazine-1,2-dicarboxylate (3b)[5]
White solid; yield: 117 mg (70%); mp 156.5–157.8 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.95 (s, 1 H), 6.83–6.74 (m, 1 H), 5.03–4.95 (m, 2 H), 2.23–2.20 (m, 12 H), 1.33–1.15 (m, 12 H).

Diisopropyl 1-(2,4,6-Trimethoxyphenyl)hydrazine-1,2-dicarboxylate (3c)[5]
Pale-yellow solid; yield: 148 mg (80%); mp 113.1–114.8 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.94 (br s, 1 H), 6.12 (s, 1 H), 6.11 (s, 1 H), 4.96–4.93 (m, 2 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 1.30–1.14 (m, 12 H).

Diisopropyl 1-(2,5-Dimethoxyphenyl)hydrazine-1,2-dicarboxylate (3d)
Yellow oil; yield: 110 mg (65%).

IR (neat): 3302, 1721, 1509, 1376, 1226, 1109 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.11–6.83 (m, 4 H), 4.98–4.95 (m, 2 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 1.32–1.18 (m, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 153.3, 148.8, 139.2, 130.7, 115.1, 114.6, 112.0, 70.5, 69.6, 55.9, 55.8, 22.0, 21.9, 21.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{25}N_2O_6$: 341.1707; found: 341.1704.

Diisopropyl 1-(3,4-Dimethoxyphenyl)hydrazine-1,2-dicarboxylate (3e)
Yellow oil; yield: 95 mg (56%);

IR (neat): 3457, 1718, 1515, 1376, 1249, 1109 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.04–6.80 (m, 3 H), 5.02–4.98 (m, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 1.28–1.28 (m, 12 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.0, 154.6, 148.4, 147.3, 135.0, 116.52, 110.5, 109.1, 70.5, 69.8, 55.8, 55.7, 21.8, 21.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{25}N_2O_6$: 341.1707; found: 341.1703.

Diisopropyl 1-(1-Naphthyl)hydrazine-1,2-dicarboxylate (3f)[2c]
Pale-yellow solid; yield: 133 mg (81%); mp 123.0–124.8 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00–7.99 (m, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.81 (d, *J* = 8.5 Hz, 1 H), 7.72–7.43 (m, 5 H), 5.01–4.98 (m, 2 H), 1.34–1.06 (m, 12 H).

Diisopropyl 1-(4-Methoxy-1-naphthyl)hydrazine-1,2-dicarboxylate (3g)[5]
Yellow solid; yield: 156 mg (87%); mp 148.1–150.0 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.0 Hz, 1 H), 7.88 (d, *J* = 7.0 Hz, 1 H), 7.65–7.46 (m, 3 H), 7.37 (s, 1 H), 6.76 (d, *J* = 8.5 Hz, 1 H), 5.06–4.98 (m, 2 H), 3.98 (s, 3 H), 1.34–1.01 (m, 12 H).

Diisopropyl 1-(5-Iodo-2-methoxyphenyl)hydrazine-1,2-dicarboxylate (3h)
Yellow solid; yield: 87 mg (40%); mp 120.2–121.9 °C

IR (neat): 3440, 1722, 1494, 1376, 1246, 1108 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (br s, 1 H), 7.57–7.55 (m, 1 H), 7.02 (br s, 1 H), 6.67 (d, *J* = 8.8 Hz, 1 H), 5.00–4.94 (m, 2 H), 3.81 (s, 3 H), 1.32–1.26 (m, 12 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.4, 154.7, 138.1, 137.9, 131.7, 114.1, 113.4, 81.6, 70.8, 69.8, 55.7, 22.0, 21.9, 21.8, 21.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}IN_2O_5$: 437.0568; found: 437.0570.

Dibenzyl 1-Mesitylhydrazine-1,2-dicarboxylate (3i)
Yellow solid; yield: 175 mg (84%); mp 139.5–141.1 °C

IR (neat): 3281, 1760, 1721, 1339, 1222, 1058 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.16 (m, 11 H), 6.84 (s, 2 H), 5.21–5.09 (m, 4 H), 2.29–2.18 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 155.9, 138.1, 136.0, 135.9, 135.8, 135.4, 129.4, 129.2, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.8, 68.3, 67.7, 20.9, 18.1, 18.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{27}N_2O_4$: 419.1965; found: 419.1964.

Dibenzyl 1-(3,4-Dimethoxyphenyl)hydrazine-1,2-dicarboxylate (3j)
Yellow solid; yield: 122 mg (56%); mp 132.1–133.8 °C

IR (neat): 3308, 1722, 1514, 1391, 1249, 1027 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 10 H), 6.96 (br s, 2 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 5.20 (s, 2 H), 5.16 (s, 2 H), 3.84 (s, 3 H), 3.78–3.58 (m, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.1, 155.0, 148.6, 147.9, 135.6, 135.4, 134.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 116.7, 110.6, 109.6, 68.3, 67.8, 55.9, 55.8.

HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{24}H_{23}N_2O_6$: 435.1562; found: 435.1556.

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