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Iron-Promoted Decarboxylation of Arylacetic Acids for the Synthesis of Aromatic Nitriles with Sodium Nitrite as the Nitrogen Source

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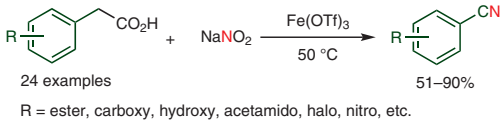

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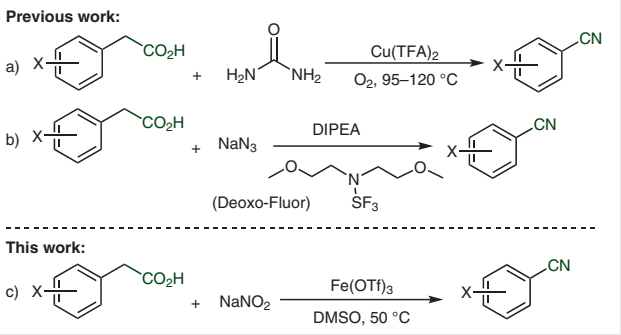
Abstract A new and effective method was developed for the synthesis of aromatic nitriles from arylacetic acids by using $NaNO_2$ as the nitrogen source and $Fe(OTf)_3$ as the promoter at 50 °C. A series of arylacetic acids underwent this transformation to give the targeted products in yields of 51–90%. Because of the mild conditions, the reaction is compatible with a broad range of functional groups, including ester, carboxy, hydroxy, acetamido, halo, nitro, cyano, methoxy, and even highly reactive formyl groups.

Key words aryl nitriles, nitriles, decarboxylation, sodium nitrite, iron catalysis, arylacetic acids

Aromatic nitriles are a group of chemicals with a wide range of synthetic uses due ease with which the cyano group can be converted into many other functional groups, such as carboxy, amino, aldehyde, or heterocyclic groups.[1] This has inspired many organic chemists to strive to develop effective methods for the preparation of aromatic nitriles.[2] Aromatic nitriles are usually synthesized from such substrates as arenediazonium salts,[3] aryl halides,[4] aldehydes,[5] amines,[6] oximes,[7] arenes,[8] amides,[6b,9] azides,[10] or ketones,[11] among others.[12]

Arylacetic acids are an attractive group of substrates because of their ready availability.[13] Song and co-workers reported a copper-catalyzed method in which the arylacetic acid undergoes decarboxylation to give an aromatic aldehyde that undergoes oxidative condensation with ammonia formed by decomposition of urea (Scheme 1a).[14] Kangani et al. used sodium azide/Deoxo-Fluor as a reagent system to synthesize aromatic nitriles from arylacetic acids (Scheme 1b).[15] However, the use of extremely poisonous sodium azide and expensive Deoxo-Fluor restricts the application of this latter method. Moreover, the former copper-catalyzed method requires high temperatures of 95–120 °C. To overcome these disadvantages, we attempted to develop a new and simple method for the synthesis of aromatic nitriles from arylacetic acids by using $NaNO_2$ as the nitrogen source (Scheme 1c). To the best of our knowledge, there is no previous example of the use of $NaNO_2$ as a nitrogen source in the conversion of arylacetic acids into aromatic nitriles.



Scheme 1 Methods for the conversion of arylacetic acids to aromatic nitriles

Our initial study was aimed at the conversion of biphenyl-4-ylacetic acid (**1a**) into biphenyl-4-carbonitrile (**2a**) as a model reaction to establish the feasibility of using $NaNO_2$ as a reagent. The reaction did not occur in the absence of a promoter (Table 1, entry 1). When $AlCl_3$ was used as the promoter, only 5% of biphenyl-4-carbonitrile (**2a**) was obtained (entry 2). Nitrile **2a** was also obtained in a low yield with $NiCl_2$, $BiCl_3$, or HCl as the promoter (entries 3–5). However, the substrate was smoothly converted into biphenyl-4-carbonitrile (**2a**) in 76% yield when $FeCl_3$ was used as the promoter (entry 6), which prompted us to screen various Fe salts. Among the screened promoters, $Fe(OTf)_3$ was the most effective, giving nitrile **2a** in 90% yield (entry 11), accompanied by a small amount of biphenyl-4-carbalde-

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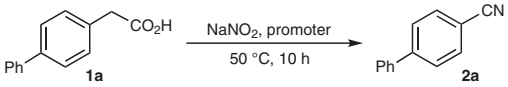
hyde as a byproduct. The reaction was highly dependent on the solvent. Reactions in dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), or *N*-methyl-2-pyrrolidone (NMP) gave nitrile **2a** in yields of 90, 59, and 76%, respectively (entries 11–13), whereas 1,4-dioxane, toluene, acetonitrile, and tetrahydrofuran (THF) were less effective as solvents (entries 14–17). The reaction temperature also had a significant effect on the reaction, and a 90% yield was obtained when the reaction was performed at 50 °C (entry 11), whereas at 30 °C, the nitrile **2a** was obtained in a lower yield of 52% (entry 18). Increasing the reaction temperature to 90 °C (entry 20) resulted in complete conversion, but the yield of nitrile **2a** decreased to 62% due to the formation of large amounts of various byproducts, including biphenyl-4-carbaldehyde, biphenyl-4-carboxylic acid, and biphenyl-4-carboxamide. These results indicated that 50 °C is the optimal reaction temperature in terms of the yield. We tried gradually reducing the promoter loading to 0.8 or 0.5 equivalents, but found that this was not possible without sacrificing product yield, even when the reaction time was prolonged to 40 hours. Although it was found to be unnecessary to use a dried solvent (entries 11 and 21), the addition of a larger amount of water had a markedly negative effect on the reaction (entry 22). In addition, we found that it was necessary to perform the reaction under an inert atmosphere (entries 23 and 24).

Having determined the optimal conditions for the reaction, we evaluated the substrate scope of the protocol for the conversion of arylacetic acids into aromatic nitriles (Scheme 2). A series of phenylacetic acids were smoothly converted into the corresponding nitriles in moderate to high yields.[16] The conditions were compatible with a broad range of functional groups, including ester, carboxy, hydroxy, acetamido, halo, nitro, cyano, and methoxy groups (**2b–n**); even the highly reactive formyl group was tolerated (**2i**). However, the reaction was susceptible to steric hindrance; for example, (4-chlorophenyl)acetic acid (**1c**) gave the corresponding product **2c** in 85% yield whereas (2-chlorophenyl)acetic acid (**1d**) gave product **2d** in only 46% yield. The electronic effect of substituents on the reaction was inconspicuous; for example, (4-bromophenyl)acetic acid (**1e**) gave product **2e** in 76% yield, whereas product **2m** was obtained in a similar yield (73%) from (4-methoxyphenyl)acetic acid (**1m**). Naphthylacetic acids were also good substrates; 2- and 1-naphthylacetic acids were smoothly converted in the corresponding naphthonitriles **2o** and **2p** in moderate yields of 75 and 69%, respectively. The heterocyclic acids 2-thienylacetic acid (**1q**) and 2-furylacetic acid (**2r**) were also smoothly converted into the corresponding products **2q** and **2r** in yields of 77 and 68% respectively.

Initially, on the basis of reports in the literature,[17] we surmised that (2*Z*)-(hydroxyimino)(phenyl)acetic acid (**3**) might be an intermediate in the present reaction of acid **1b**. Indeed, this intermediate was observed in the reaction of

Table 1 Optimization of the Conversion of Biphenyl-4-ylacetic Acid (**1a**) into Biphenyl-4-carbonitrile (**2a**)[a]

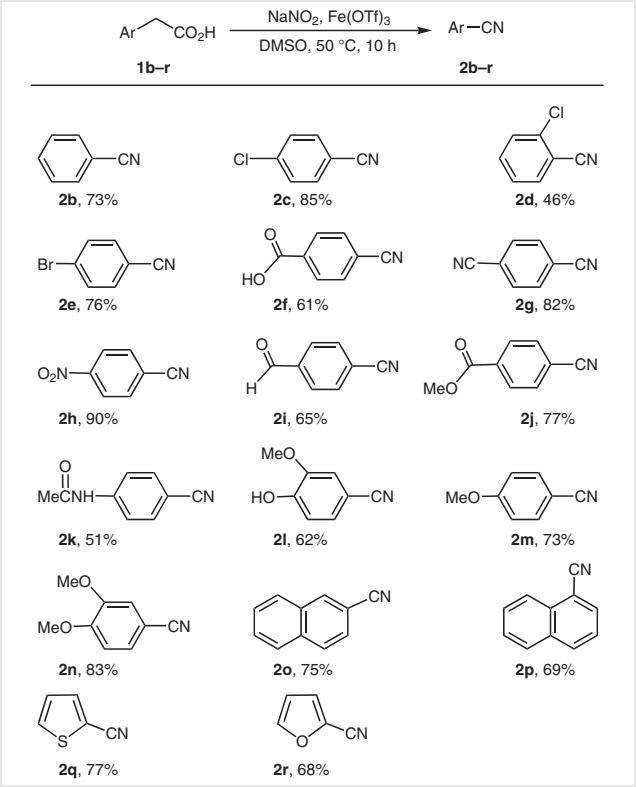


Entry	Promoter	Solvent	Temp (°C)	Conversion[b] (%)	Yield[b] (%)
1	–	DMSO	50	2	0
2	$AlCl_3$	DMSO	50	7	5
3	$NiCl_2$	DMSO	50	28	22
4	$BiCl_3$	DMSO	50	15	13
5	HCl[c]	DMSO	50	12	7
6	$FeCl_3$	DMSO	50	79	76
7	$Fe(acac)_3$	DMSO	50	7	6
8	$FeSO_4$	DMSO	50	60	52
9	ferrocene	DMSO	50	28	25
10	γ-Fe_2O_3	DMSO	50	27	22
11	**$Fe(OTf)_3$**	**DMSO**	50	**97**	**90**
12	$Fe(OTf)_3$	DMF	50	63	59
13	$Fe(OTf)_3$	NMP	50	78	76
14	$Fe(OTf)_3$	1,4-dioxane	50	33	31
15	$Fe(OTf)_3$	toluene	50	15	11
16	$Fe(OTf)_3$	MeCN	50	7	6
17	$Fe(OTf)_3$	THF	50	3	2
18	$Fe(OTf)_3$	DMSO	30	53	52
19	$Fe(OTf)_3$	DMSO	70	98	71
20	$Fe(OTf)_3$	DMSO	90	100	62
21[d]	$Fe(OTf)_3$	DMSO	50	95	87
22[e]	$Fe(OTf)_3$	DMSO	50	81	36
23[f]	$Fe(OTf)_3$	DMSO	50	100	81
24[g]	$Fe(OTf)_3$	DMSO	50	100	39

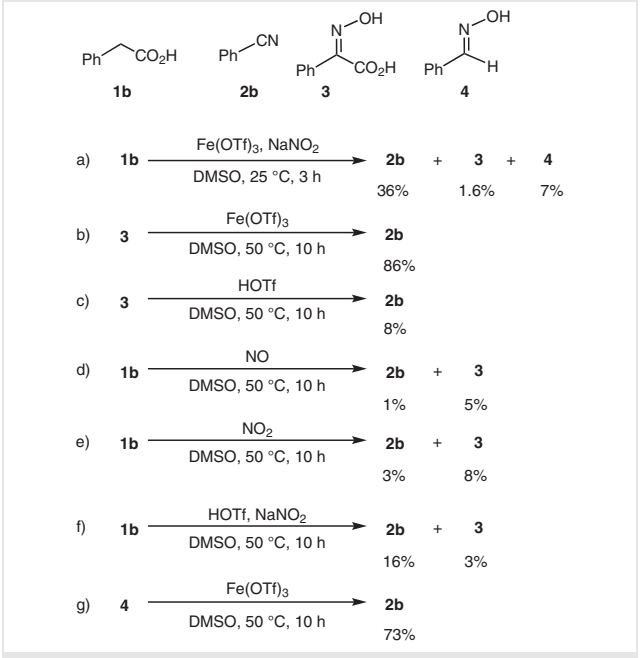
[a] Reaction conditions: **1a** (0.5 mmol), $NaNO_2$ (3 mmol), promoter (1 mmol), solvent (2 mL), 10 h, under argon. The solvents were undried.
[b] Determined by GC with biphenyl as an internal standard.
[c] 12 M aq HCl.
[d] Anhyd DMSO.
[e] H_2O (0.2 mL) was added.
[f] Under air.
[g] Under O_2.

1b (Scheme 3a), and it could be converted into benzonitrile (**2b**) under our reaction conditions (Scheme 3b).[17b] In addition, the experimental results shown in Schemes 3b and 3c suggest that the presence of Fe^{3+} is necessary for the effective conversion of intermediate **2c** into benzonitrile (**2b**).

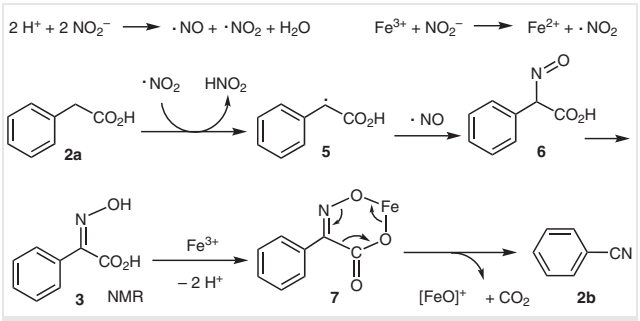
We therefore initially proposed the mechanism shown in Scheme 4.[17] First, NO_2, formed by the reaction of the nitrite ion with the acid, abstracts a benzylic hydrogen atom from phenylacetic acid (**2a**) to give the benzylic radical **5**, which reacts with NO to form intermediate **6**. Intermediate **6** then undergoes the tautomerization to the oxime inter-



Scheme 2 Conversion of various arylacetic acids into nitriles. *Reagents and conditions*: **1** (0.5 mmol), $NaNO_2$ (3 mmol), $Fe(OTf)_3$ (1 mmol), DMSO (2 mL), 50 °C, 10 h, under argon. The DMSO was not dried, and the air in the tube was removed. The yields of **2b**, **2q**, and **2r** are GC yields, whereas the other yields are isolated yields.



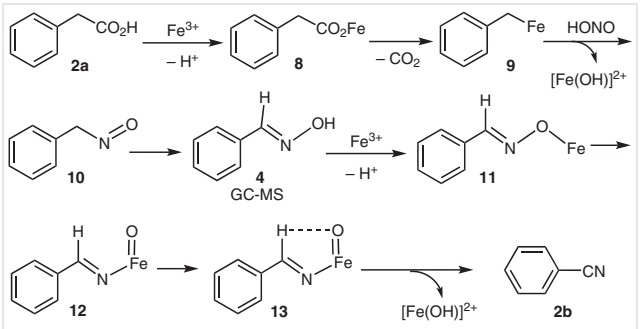
Scheme 3 Control experiments for mechanistic investigation



Scheme 4 Minor mechanistic pathway for the present reaction

mediate **3**. This intermediate is converted into benzonitrile (**2b**) with the assistance of Fe^{3+}. This pathway suggests that a large amount of (*Z*)-2-(hydroxyimino)-2-phenylacetic acid (**3**) should be formed by the reaction between NO_2 and phenylacetic acid in the absence of a Fe salt. However, this intermediate was obtained in low yields in the presence of NO_2, NO, or H^+/NO_2^- (Schemes 3d–f), suggesting that the radical pathway shown in Scheme 4 is not the major pathway. This is consistent with the experimental finding that neither of the radical inhibitors TEMPO and BHT completely inhibited the formation of benzonitrile (see Scheme S2 in the Supporting Information).

As shown in Scheme 3a, the present reaction gave the oxime **4** in 7% yield. Moreover, this intermediate underwent dehydration to give benzonitrile (**2b**) in a high yield in the presence of $Fe(OTf)_3$ (Scheme 3g). These results show that the mechanistic pathway involves the formation and dehydration of oxime **4**. Based on the observations discussed above and reports in the literature,[18] we tentatively propose the mechanistic pathway shown in Scheme 5. Phenylacetic acid (**2a**) undergoes decarboxylation with the assistance of Fe^{3+} to give intermediate **9**. The reaction of intermediate **9** with nitrous acid gives (nitrosomethyl)benzene (**10**), which tautomerizes to the oxime **4**. This reacts with Fe^{3+} to produce intermediate **11**, which eventually rearranges the intermediate **13**, stabilized by an intramolecular hydrogen bond. Finally, **13** decomposes to give the target product **2b**.



Scheme 5 Major mechanistic pathway for the present reaction

In conclusion, we have developed a new and effective method for the synthesis of aromatic nitriles from arylacetic acids by using $NaNO_2$ as a nitrogen source and $Fe(OTf)_3$ as a promoter at 50 °C. To our knowledge, there is no previous example of the use of $NaNO_2$ as a nitrogen source in the conversion of arylacetic acids into aromatic nitriles. The mild conditions permit the reaction to be compatible with a broad range of functional groups, such as ester, carboxy, hydroxy, acetamido, halo, nitro, cyano, methoxy, and even the highly reactive formyl group. Under the present condition, a series of phenylacetic acids and naphthylacetic acids, as well as 2-furylacetic acid and 2-thienylacetic acid, were smoothly converted into the corresponding nitriles in low to high yields.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707300.

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(16) **Nitriles 2a–r: General Procedure**

A tube of approximate volume 45 mL was charged with the appropriate arylacetic acid (0.5 mmol), $NaNO_2$ (3 mmol), $Fe(OTf)_3$ (1 mmol), and undried DMSO (2 mL), and the air in the tube was replaced by argon gas. The tube was sealed and the mixture was heated with magnetic stirring at 50 °C for 10 h, then cooled to r.t. The solvent was evaporated, and the residue was purified by column chromatography (silica gel).

Biphenyl-4-carbonitrile (2a)[11b]

White solid; yield: 77.1 mg (86%); m.p. 84–86°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.4 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.61–7.63 (m, 2 H), 7.50–7.53 (m, 2 H), 7.44–7.48 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 139.2, 132.6, 129.1, 128.7, 127.8, 127.3, 119.0, 110.9.

Methyl 4-Cyanobenzoate (2j)[5b]

White solid; yield: 62 mg (77%); m.p. 63–65°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.1 Hz, 2 H), 7.76 (d, *J* = 8.1 Hz, 2 H), 3.97 (s, 3 H).

C NMR (100 MHz, $CDCl_3$): δ = 165.4, 133.9, 132.2, 130.1, 118.0, 116.4, 52.7.

1-Naphthonitrile (2p)[5b]

White solid; yield: 52.8 mg (69%); m.p. 37–39°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.3 Hz, 1 H), 8.09 (d, *J* = 8.3 Hz, 1 H), 7.93 (t, *J* = 7.6 Hz, 2 H), 7.71 (t, *J* = 7.0 Hz, 1 H), 7.64 (t, *J* = 7.2 Hz, 1 H), 7.54 (t, *J* = 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.7, 134.2, 132.3, 129.2, 129.1, 128.4, 128.1, 127.7, 126.4, 119.3, 109.4.

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