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Formation of Amides from Imines via Cyanide-Mediated Metal-Free Aerobic Oxidation

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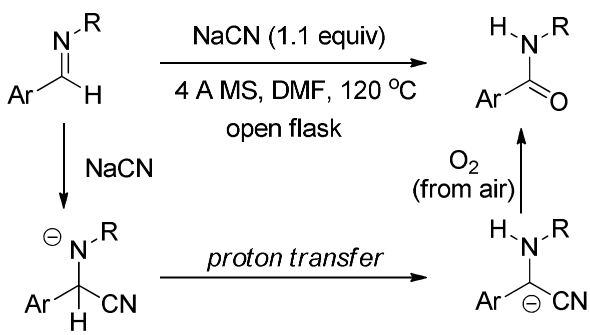


Abstract: A new protocol for the direct formation of amides from imines derived from aromatic aldehydes via metal-free aerobic oxidation in the presence of cyanide is described. This protocol was applicable to various aldimines and the desired amides were obtained in moderate to good yields. Mechanistic studies suggested that this aerobic oxidative amidation might proceed via the addition of cyanide to imines followed by proton transfer from carbon to nitrogen in the original imines leading to carbanions of α-aminonitriles, which undergo subsequent oxidation with molecular oxygen in air to provide the desired amide compounds.

‡ These authors contributed equally.

Introduction

Ever since Strecker's original report in 1850 on the three component reaction between aldehydes, ammonia, and hydrogen cyanide (HCN),[1] the addition of HCN to imines derived from carbonyls and amines leading to α-aminonitriles has been the subject of great interest because the resulting Strecker products **I** have been widely used as versatile intermediates in a number of synthetic applications (Figure 1a).[2,3] Although a similar addition of cyanide anion (CN^-) to imines has been known for a long time, synthetic protocols utilizing the resulting cyanide adducts **II** as synthetic intermediates have been far less developed than those with HCN adducts **I**. This might be due to the fact that cyanide adducts **II** readily undergo an elimination reaction (retro-Strecker reaction), which makes it difficult to maintain high concentration of adducts **II** so that the rate of their conversion to the next step is reasonably high (Figure 1b).[4]

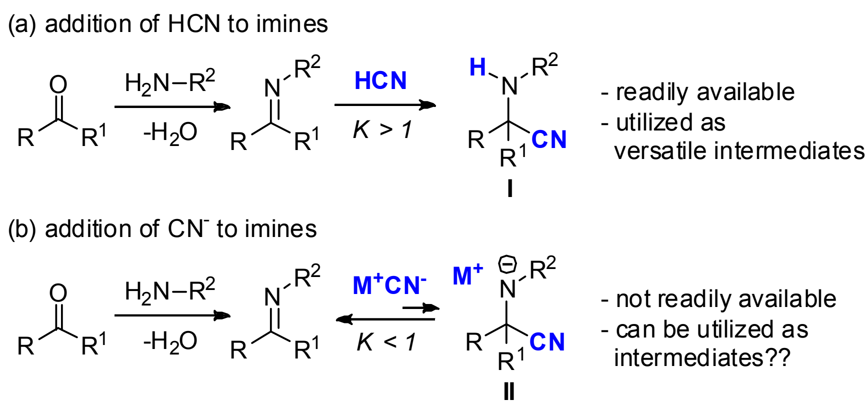
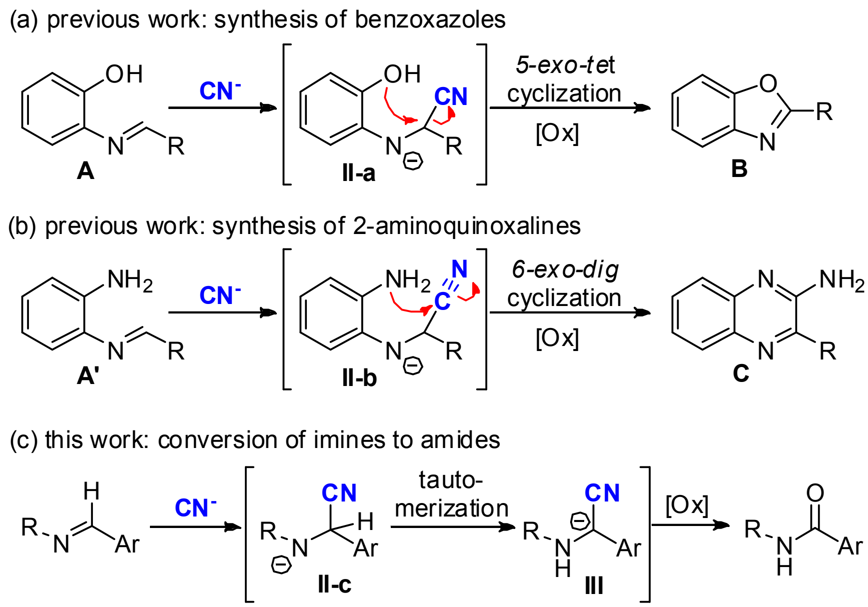


Figure 1. Comparison of the Addition Products of HCN and CN^- to Imines

Recently, our group initiated a program to develop novel synthetic protocols utilizing cyanide adducts **II** as valuable synthetic intermediates. For example, we developed a protocol for the synthesis of benzoxazoles from *ortho*-aminophenol and aldehydes via metal-free aerobic oxidative cyclization using cyanide as the catalyst (Scheme 1a).[5] Imine **A** is unlikely to undergo cyclization because *5-endo-trig* cyclization is disfavored according to Baldwin's rules.[6] However, cyanide adduct **II-a** readily underwent cyclization through favored 5-*exo-tet* cyclization, and subsequent aerobic oxidation of the cyclized product provided benzoxazole **B**. When we attempted to extend this method to the synthesis of benzimidazoles with *ortho*-phenylenediamine, intermediate **II-b** underwent 6-*exo-dig* cyclization rather than the expected 5-*exo-tet* cyclization leading to the formation of 2-aminoquinoxaline **C** after aerobic oxidation (Scheme 1b).[7]

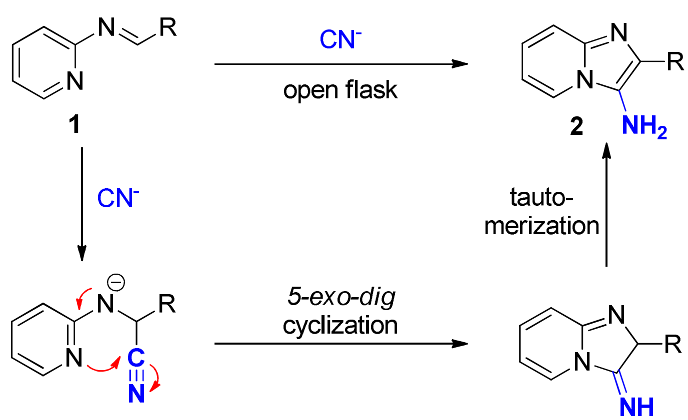


Scheme 1. Synthetic Applications of Cyanide Adducts **II** to Organic Transformations via Aerobic Oxidation.

Herein we report the development of another synthetic protocol using cyanide adducts **II** as the intermediates: the direct formation of amides from imines via metal-free aerobic oxidation (Scheme 1c).[8-11] This result is based on our recent finding of the unexpected formation of amides from aromatic aldimines in the presence of cyanide, when we attempted to utilize cyanide as a surrogate for isocyanide in the synthesis of imidazopyridines. Mechanistic studies suggested that cyanide adducts **II-c** underwent tautomerization to generate benzylic anions **III**,[12] and subsequent aerobic oxidation of **III** provided the corresponding amides.

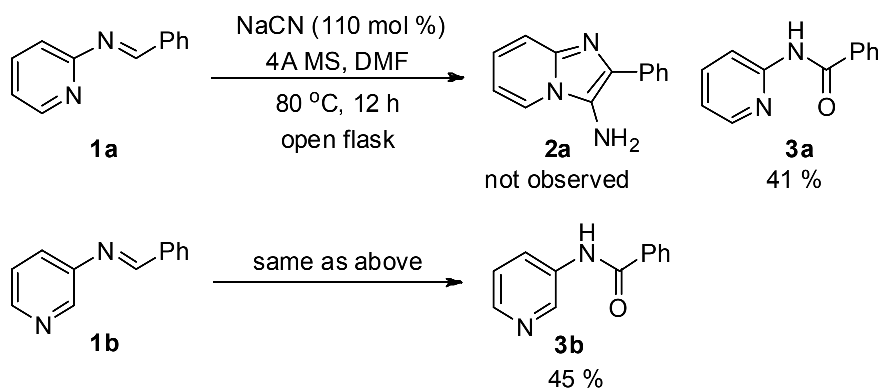
Results and Discussion

Since we demonstrated that cyanide could be utilized as a surrogate for isocyanide in the synthesis of 2-aminoquinoxalines (Scheme 1b),[7,13] we attempted to extend the usage of cyanide as a surrogate for isocyanide to the synthesis of other nitrogen-containing heteroaromatic compounds, such as imidazopyridine **2**.[14] For example, it was expected that imidazopyridine **2** could be prepared from imine **1**, derived from 2-aminopyridine and aldehyde, using cyanide as a surrogate for isocyanide via addition of cyanide to imine **1** followed by *5-exo-dig* cyclization (Scheme 2).



Scheme 2. Application of CN^- as a Surrogate for Isocyanide in the Synthesis of Imidazopyridine **2**.

Based on this idea, imine **1a**, derived from 2-aminopyridine and benzaldehyde, was subjected to the aerobic oxidative cyclization conditions[7] previously used for the synthesis of 2-aminoquinoxalines. However, the expected imidazopyridine **2a** was not observed; rather unexpectedly, amide **3a** was obtained as the major product (Scheme 3).[10] Because the direct conversion of imines to amides via aerobic oxidation in the presence of cyanide has been rarely reported in the literature even with the assistance of metal catalysts,[11,15] we initially suspected that the nitrogen atom in the pyridine ring of **1a** might play a role in this aerobic oxidative amidation reaction. Thus, we tested the same transformation with imine **1b,** which is derived from 3-aminopyridine instead of 2-aminopyridine. When **1b** was subjected to the above conditions, the formation of the corresponding amide **3b** was again observed.

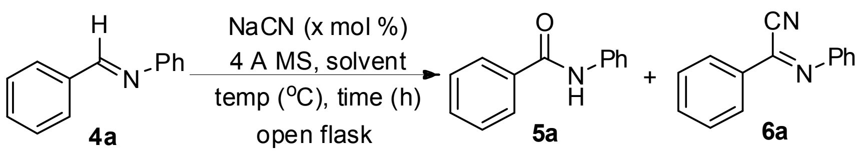


Scheme 3. Unexpected Formation of Amides from Imines

Since these results strongly suggested that the nitrogen atom in the pyridine ring in imine **1** is not required for the formation of amides from imines, the reaction conditions were optimized using imine **4a**, derived from aniline and benzaldehyde, as a model compound (Table 1). Cyanide was found to play a crucial role in this protocol; amide **5a** was obtained in good yield in the presence of cyanide, whereas the amide formation did not occur at all in the absence of cyanide (entries 1 and 2). When this reaction was performed under an argon atmosphere, a negligible amount of **5a** was observed, indicating that molecular oxygen in air is the terminal oxidant in this transformation (entry 3). The choice of solvent was found to have a strong influence on the formation of 5**a** (entries 1, and 4-8). Among the solvents tested, **5a** was obtained in the best yield in DMF, and thus, DMF was chosen for further investigations.

Next, the effect of the amount of cyanide on the formation of **5a** was examined (entries 1, 2, and 9-11). The amount of cyanide was found to exert a strong influence on the efficacy of this transformation. The yield of **5a** increased with the amount of cyanide until a stoichiometric amount of cyanide was used. However, the yield of **5a** did not improve further and reached a plateau when super-stoichiometric amounts of cyanide were used. Thus, we decided to use a slight excess of cyanide (110 mol %) as the optimal amount.

Table 1. Optimization of Reaction Conditions



entry	NaCN (x mol %)	solvent	Temp (°C)	time (h)	yield of **5a** (%)[a]
1	110	DMF	80	4	69
2	-	DMF	80	24	N.R.[b]
3[c]	110	DMF	80	24	< 5
4	110	DMSO	80	4	56
5	110	CH_3CN	80	24	40
6	110	dioxane	80	24	N.R.[b]
7	110	toluene	80	24	N.R.[b]
8	110	*i*-PrOH	80	24	N.R.[b]
9	50	DMF	80	8	35
10	200	DMF	80	4	74
11	300	DMF	80	4	70
12	110	DMF	100	2	71 (13)[d]
13	110	DMF	120	1	70 (12)[d]

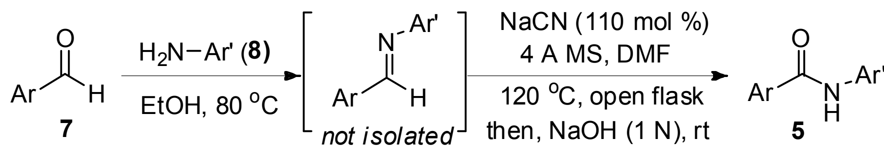
14	110	DMF	120	2	81[e]
15[f]	110	DMF	120	2	79

[a] Isolated yield. [b] No Reaction. [c] Under an argon atmosphere. [d] The number in parenthesis is the isolated yield of **6a**. [e] The isolated yield of **5a** after basic hydrolysis. [f] Sequential one-pot protocol.

Despite numerous effects, we were not able to further improve the yield of **5a** higher than 70% yield, and a careful analysis of the reaction mixture revealed that α-iminonitrile **6a**[16] was also formed albeit in low yield. Because α-iminonitriles could be converted to the corresponding amides via hydrolysis,[17] we attempted to convert **6a** into **5a** at the elevated reaction temperature (entries 1, 12, and 13). Rather disappointingly, the yield of **5a** did not improve, and **6a** was still obtained in similar yields even at higher temperatures, although the reaction rate accelerated at high temperature. However, when the reaction mixture was treated with a NaOH solution after complete consumption of **4a**, **5a** was obtained in 81% yield (entry 14). Finally, we further developed a one-pot protocol for the synthesis of **5a** directly from the aldehyde and aniline without isolation of imine **4a**. When **4a**, prepared in situ from benzaldehyde and aniline, was subjected to the standard aerobic oxidation conditions, the yield of **5a** was similar to that obtained using isolated imine **4a,** after treatment of the reaction mixture with an aqueous basic solution (entry 15).[18]

With these optimized conditions in hand, we explored the substrate scope for this transformation (Table 2). Various aromatic aldehydes could be applied to this protocol, and amides **5** were obtained in good yields (entries 1-9). The electronic properties of the aldehydes exerted some influence on this transformation; aldehydes bearing electron donating groups (entries 2 and 3) provided the corresponding amides in better yields than those with electron withdrawing substituents (entries 4-6). More sterically hindered *ortho*-substituted aldehydes were also amenable to this protocol, and the corresponding amides **5** were obtained in good yields (entries 7–9). This protocol was further extended to fused aromatic aldehydes and heteroaromatic aldehydes, and the desired products were obtained in moderate to good yields (entries 10-14). Next, we investigated the effect of the electronic properties of aniline derivatives on this transformation (entries 1, 15 and 16). The electronic nature of anilines was found to have only small influence on the yield of this transformation; aniline derivatives bearing either electron-rich or electron-deficient substituents provided the desired products in slightly lower yields than aniline itself.

Table 2. Substrate Scope

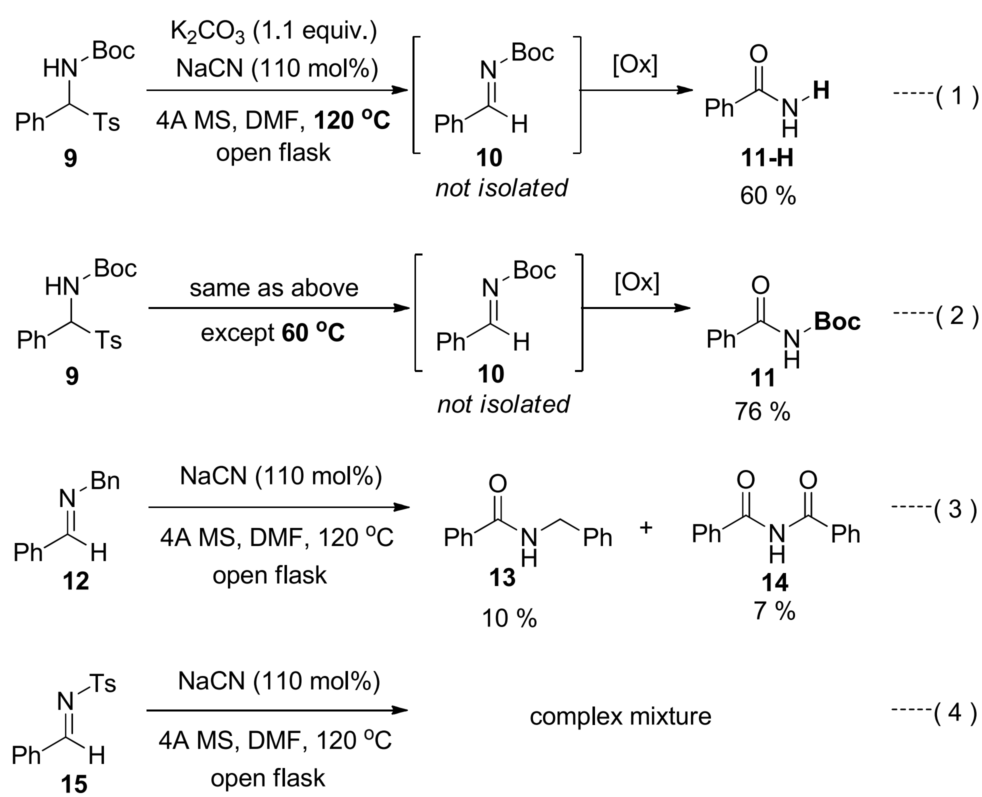


entry	Amide (**5**)	Ar	Ar’	yield (%)[a]
1	**5a**	C_6H_5	Ph	79
2	**5b**	4-MeOC_6H_4	Ph	76
3	**5c**	4-MeC_6H_4	Ph	67
4	**5d**	4-ClC_6H_4	Ph	60
5	**5e**	4-BrC_6H_4	Ph	57
6	**5f**	4-Me$CO_2C_6H_4$	Ph	77
7	**5g**	2-MeOC_6H_4	Ph	71
8	**5h**	2-MeC_6H_4	Ph	81
9	**5i**	2-ClC_6H_4	Ph	64
10	**5j**	1-Naphthyl	Ph	69
11	**5k**	2-Naphthyl	Ph	56

12	**5l**	2-Furyl	Ph	48
13	**5m**	2-Thienyl	Ph	71
14	**5n**	2-Pyridinyl	Ph	83
15	**5o**	C_6H_5	4-BrC_6H_4	65
16	**5p**	C_6H_5	4-MeOC_6H_4	62

[a]Isolated yield.

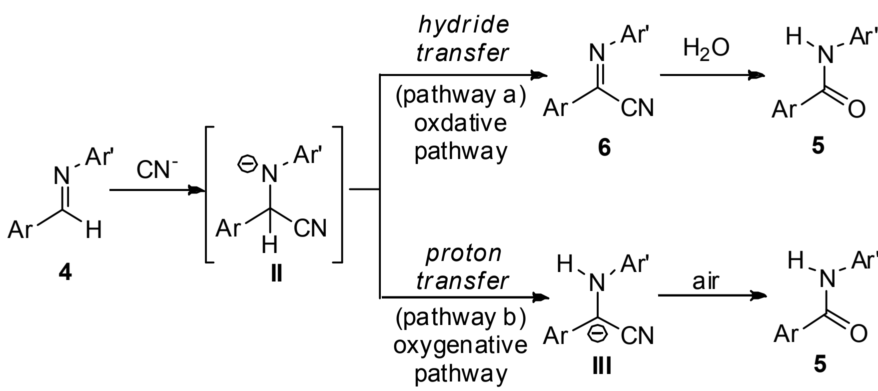
We further investigated other imines derived from different amines than anilines for this aerobic oxidative amidation reaction (Scheme 4). When a precursor **9** of Boc imine **10** was subjected to the standard conditions in the presence of K_2CO_3, the corresponding Boc imine **10** in situ generated readily underwent the oxidative amidation reaction, but the Boc group in the resulting amide **11** was removed to provide benzamide **11-H** in 60% yield (eq. 1).



Scheme 4. Investigation of Amine Sources

However, when the same transformation was performed at 60 °C, the desired Boc protected amide **11** was obtained in 76% yield without any concomitant formation of **11-H** (eq. 2).[20] Unfortunately, however, other imines derived from other amine sources, such benzyl amine and tosyl amine, were found not to be applicable to this aerobic oxidative amidation; benzyl imine **12** afforded the corresponding amide **13** and imide **14** only in low yields (~10%) (eq. 3), while tosyl imine **15** provided a complex mixture (eq. 4).

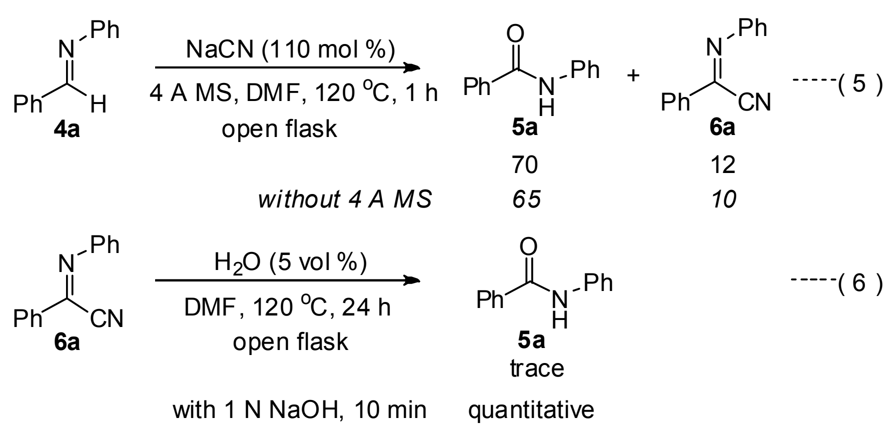
With these results in hand, we attempted to elucidate the reaction mechanism for this cyanide-mediated aerobic oxidative amidation of imines. As cyanide was found to play a critical role in this transformation, cyanide adduct **II** might be the key intermediate. From intermediate **II**, there might be two possible reaction pathways for the aerobic oxidative amidation reaction (Scheme 5).[19]



Scheme 5. Possible Reaction Pathways

Intermediate **II** might first undergo oxidation through hydride transfer to form α-iminonitrile **6**, with subsequent hydrolysis of **6** affording the desired amide **5** (pathway a; oxidative pathway). On the other hand, proton transfer from the α-carbon atom to the nitrogen atom in intermediate **II** might take place to generate anion **III**,[12] which subsequently undergoes reaction with molecular oxygen to furnish amide **5** (pathway b; oxygenative pathway).[18,19(b)]

Since the formation of α-iminonitriles **6** was observed during the optimization of the reaction conditions, we initially suspected that amides **5** might be formed through hydrolysis of α-iminonitriles **6**[17]. Under such a scenario, it was expected that water would play a role in this transformation. To test this idea, we carried out a few controlled experiments (Scheme 6). When the reaction was performed in the absence of molecular sieves (i.e., in the presence of water), the yield of **5a** was not improved, and **5a** and **6a** were obtained in similar level of yields regardless of the presence of molecular sieves (eq. 5). Furthermore, when the isolated α-iminonitrile **6a** was directly subjected to hydrolysis in wet organic solvent, **6a** did not undergo the hydrolysis at 120 °C even after 24 h (eq. 6). Instead, strong basic conditions (1 N NaOH) were needed to hydrolyze α-iminonitrile **6a** into amide **5a**. These results led us to rule out the possibility that the amides would be formed via the hydrolysis of α-iminonitriles even though **6** was observed in the reaction mixture. Based on these experimental results in conjunction with the previous reports on dimerization of aldimines where intermediate **III** was considered to be formed from cyanide adduct **II** via tautomerization,[12,15] we believe that the formation of amides from imines in the presence of cyanide would proceed via pathway *b*.



Scheme 6. Test of Iminonitrile **4a** as an Intermediate in the Aerobic Oxidative Amidation

Conclusions

In conclusion, we reported the direct formation of amides from imines in the presence of cyanide via metal-free aerobic oxidation. Various aromatic aldehydes were applicable to this protocol and the desired amides were obtained in good to high yields. Furthermore, other imines derived from other amine sources than aniline could be applied to this protocol although the yields of the corresponding amides showed a dependence on the choice of amines. Mechanistic studies suggested that this aerobic oxidative amidation might proceed via the addition of cyanide to imines, followed by the proton transfer leading to carbanions of α-aminonitriles, and subsequent aerobic oxidation. The elucidation of the detailed reaction mechanism and further application of this method are currently underway in our laboratory.

Experiment Section

General. All reactions were carried out in oven- or flame-dried glassware in an open flask unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using pre-coated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm), with combination of potassium permanganate and/or phosphomolybdic acid solution as an indicator. Flash column chromatography was performed using silica gel 60 (230 – 400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Commercial grade reagents and solvents were used without further purification. Liquid aldehydes were purified by fractional distillation and solid aldehydes were purified by a column chromatography on silica. ^{1}H NMR spectra were recorded on either a 300 or 400 MHz spectrometer. Tetramethylsilane (δ: 0.0 ppm) was used as an internal standard for ^{1}H NMR. The proton spectra are reported as follows δ (position of proton, multiplicity, coupling constant J, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad).

General procedure for metal-free aerobic oxidative amidation (Table 2). To a 50 mL two-necked round bottomed flask equipped with a condenser were added amine **8** (1.1 mmol, 1.1 equiv.) and ethanol (10 mL). To the above solution was added aryl aldehyde **7** (1.0 mmol, 1.0 equiv.), and the reaction mixture was allowed to stirred at 80 °C and monitored by TLC. After complete consumption of aldehyde **7**, the reaction mixture was concentrated under reduced pressure to afford the crude product of imine. Without further purification of the resulting imine, the crude mixture was dissolved in DMF (10 mL), and sodium cyanide (1.1 mmol, 1.1 equiv.) and molecular sieves were added to the reaction mixture. Then, the reaction mixture was stirred at 120 °C until all the imine was completely consumed. On the complete consumption of the imine, NaOH solution (1.0 N) was added to the reaction mixture and the reaction mixture was allowed to stir at room temperature for 10 min. The crude mixture was extracted with ether and the organic layer was combined, dried over $MgSO_4$, and concentrated. The resulting crude mixture was purified by flash column chromatography on silica to provide the expected amide **5**.

N-(Pyridin-2-yl)benzamide (**3a**)

The desired product **3a** was obtained as a yellow solid (81 mg, 41% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:2): R_f = 0.50 (ethyl acetate/hexanes = 2:1). The spectroscopic data were in good agreement with the literature.[21] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.77 (br, 1H), 8.38 (d, J = 4.1 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 8.0 Hz, 2H), 7.83 (t, J = 7.7 Hz, 1H), 7.46 - 7.62 (m, 4H).

N-(Pyridin-3-yl)benzamide (**3b**)

The desired product **3b** was obtained as a yellow solid (85 mg, 45% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:4): R_f = 0.30 (ethyl acetate/hexanes = 1:4). The spectroscopic data were in good agreement with the literature.[22] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.45 (br, 1H), 8.92 (d, J = 1.9 Hz, 1H), 8.30 (d, J = 4.7 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 7.2 Hz, 2H), 7.52-7.63 (m, 3H), 7.36 - 7.41 (m, 1H).

N-Phenylbenzamide (**5a**)

The desired product **5a** was obtained as a white solid (147 mg, 79% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.30 (ethyl acetate/hexanes = 1:5). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.24 (br, 1H), 7.94 (d, J = 7.2 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.48 - 7.62 (m, 3H), 7.34 (t, J = 7.7 Hz, 2H), 7.09 (t, J = 7.2 Hz, 1H).

4-Methoxy-N-phenylbenzamide (**5b**)

The desired product **5b** was obtained as a yellow solid (173 mg, 76% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.40 (ethyl acetate/hexanes = 1:3). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.07 (br, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 7.7 Hz, 2H), 7.32 (t, J = 7.7 Hz, 2H), 7.01 - 7.10 (m, 3H), 3.82 (s, 3H).

4-Methyl-N-phenylbenzamide (**5c**)

The desired product **5c** was obtained as a white solid (133 mg, 67% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.40 (ethyl acetate/hexanes = 1:5). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.77 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 7.7 Hz, 2H), 7.37 (t, J = 7.7 Hz, 2H), 7.29 (t, J = 7.7 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H), 2.43 (s, 3H).

4-Chloro-N-phenylbenzamide (**5d**)

The desired product **5d** was obtained as a white solid (139 mg, 60% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.30 (ethyl acetate/hexanes = 1:5). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.82 (d, J = 8.2 Hz, 2H), 7.73 (br, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.17 (t, J =7.4 Hz, 1H).

4-Bromo-N-phenylbenzamide (**5e**)

The desired product **5e** was obtained as a yellow solid (133 mg, 57% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.30 (ethyl acetate/hexanes = 1:5). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.75 (d, J = 8.2 Hz, 2H), 7.63 (dd, J = 7.8 Hz, J = 4.7 Hz, 4H), 7.39 (t, J = 7.8 Hz, 2H), 7.15 – 7.20 (m, 1H).

4-Methoxycarbonyl-N-phenyl-benzamide (**5f**)

The desired product **5f** was obtained as a yellow solid (196 mg, 77% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:4): R_f = 0.30 (ethyl acetate/hexanes = 1:4). The spectroscopic data were in good agreement with the literature.[24] ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.16 (d, J = 7.8 Hz, 2H), 7.94 (d, J = 7.8 Hz, 2H), 7.82 (br, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.19 (m, 1H), 3.97 (s, 3H).

2-Methoxy-N-phenylbenzamide (**5g**)

The desired product **5g** was obtained as a white solid (161 mg, 71% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.30 (ethyl acetate/hexanes = 1:5). The spectroscopic data were in good agreement with the literature.[24] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.10 (br, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.32 (t, J = 7.4 Hz, 2H), 7.17 (d, J = 8.3 Hz, 1H), 7.01 – 7.10 (m, 2H), 3.88 (s, 3H).

2-Methyl-N-phenylbenzamide (**5h**)

The desired product **5h** was obtained as a white solid (171 mg, 81% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:8): R_f = 0.60 (ethyl acetate/hexanes = 1:5). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.28 (br, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.24 – 7.47 (m, 6H), 7.07 (t, J = 7.3 Hz, 1H), 2.37 (s, 3H).

2-Chloro-N-phenylbenzamide (**5i**)

The desired product **5i** was obtained as a yellow solid (148 mg, 64% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.30 (ethyl acetate/hexanes = 1:5). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ.7.89 (br, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.35 – 7.48 (m, 5H), 7.18 (t, J = 7.2 Hz, 1H).

N-Phenyl-1-naphthalamide (**5j**)

The desired product **5j** was obtained as a white solid (170 mg, 69% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.30 (ethyl acetate/hexanes = 1:5). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.57 (br, 1H), 8.13 – 8.20 (m, 1H), 7.99 – 8.10 (m, 2H), 7.71 – 7.83 (m, 3H), 7.55 – 7.63 (m, 3H), 7.36 (t, J = 7.8 Hz, 2H), 7.11 (t, J = 7.3 Hz, 1H).

N-Phenyl-2-naphthalamide (**5k**)

The desired product **5k** was obtained as a yellow solid (139 mg, 56% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.30 (ethyl acetate/hexanes = 1:5). The spectroscopic data were in good agreement with the literature.[25] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.43 (br, 1H), 8.57 (s, 1H), 7.98 - 8.11 (m, 4H), 7.82 (d, J = 8.0 Hz, 2H), 7.59 - 7.66 (m, 2H), 7.37 (t, J = 7.3 Hz, 2H), 7.11 (t, J = 7.0 Hz, 1H).

N-Phenyl-furan-2-carboxamide (**5l**)

The desired product **5l** was obtained as a dark brown solid (90 mg, 48% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:4): R_f = 0.30 (ethyl acetate/hexanes = 1:4). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.17 (br, 1H), 7.92 (s, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.32 (t, J = 7.7 Hz, 3H), 7.10 (t, J = 7.4 Hz, 1H), 6.67 – 6.71 (m, 1H).

N-Phenyl-thiophen-2-carboxamide (**5m**)

The desired product **5m** was obtained as a yellow solid (144 mg, 71% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.30 (ethyl acetate/hexanes = 1:5). The spectroscopic data were in good agreement with the literature.[25] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.21 (br, 1H), 8.01 (d, J = 3.6 Hz, 1H), 7.84 (d, J = 5.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H) 7.19 - 7.24 (m, 1H) 7.09 (t, J = 7.3 Hz, 1H).

N-Phenyl picolinamide (**5n**)

The desired product **5n** was obtained as a yellow solid (164 mg, 83% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:3): R_f = 0.40 (ethyl acetate/hexanes = 1:3). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.62 (br, 1H), 8.73 (d, J = 4.1 Hz, 1H), 8.12 - 8.20 (m, 1H), 8.06 (t, J = 7.6 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.62 - 7.70 (m, 1H), 7.35 (t, J = 7.7 Hz, 2H), 7.11 (t, J = 7.2 Hz, 1H).

N-(4-Bromophenyl)benzamide (**5o**)

The desired product **5o** was obtained as a yellow solid (176 mg, 65% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:8): R_f = 0.50 (ethyl acetate/hexanes = 1:5). The spectroscopic data were in good agreement with the literature.[26] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.36 (br, 1H), 7.93 (d, J = 7.7 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.49 – 7.62 (m, 5H).

N-(4-Methoxyphenyl)benzamide (**5p**)

The desired product **5p** was obtained as a yellow solid (141 mg, 62% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:4): R_f = 0.40 (ethyl acetate/hexanes = 1:3). The spectroscopic data were in good agreement with the literature.[23] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.12 (br, 1H), 7.93 (d, J = 6.9 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.47 - 7.59 (m, 3H), 6.91 (d, J = 9.1 Hz, 2H), 3.73 (s, 3H).

Benzamide (**11-H**)

The desired product **11-H** was obtained as a white solid (72 mg, 60% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:1): R_f = 0.30 (ethyl acetate/hexanes = 1:1). The spectroscopic data were in good agreement with the literature.[9(b)] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 7.96 (br, 1H), 7.85 (d, J = 7.4 Hz, 1H), 7.47 - 7.53 (m, 1H), 7.40 - 7.47 (m, 2H), 7.35 (br, 1H).

N-(tert-Butyloxycarbonyl)benzamide (**11**)

The desired product **11** was obtained as a white solid (165 mg, 76% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:3): R_f = 0.30 (ethyl acetate/hexanes = 1:3). The spectroscopic data were in good agreement with the literature.[20] ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.66 (br, 1H), 7.82 (d, J = 7.7 Hz, 2H), 7.54 – 7.61 (m, 1H), 7.42 – 7.50 (m, 2H), 1.46 (s, 9H).

N-Benzylbenzamide (**13**)

The desired product **13** was obtained as a white solid (21 mg, 10% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.70 (ethyl acetate/hexanes = 1:1). The spectroscopic data were in good agreement with the literature.[9(a)] ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.74 – 7.84 (m, 2H), 7.29 – 7.53 (m, 8H), 6.46 (br, 1H), 4.65 (d, J = 5.5 Hz, 2H).

N,2-Diphenylacetamide **(14)**

The desired product **14** was obtained as a white solid (15 mg, 7% yield) after column chromatography on silica (ethyl acetate/hexanes = 1:5): R_f = 0.60 (ethyl acetate/hexanes = 1:1). The spectroscopic data were in good agreement with the literature.[20] ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.90 (br, 1H), 7.88 (d, J = 7.4 Hz, 4H), 7.58 – 7.67 (m, 2H), 7.52 (t, J = 7.6 Hz, 4H).

Notes

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Supporting Information

NMR spectra of all compounds . This material is available free of charge via the Internet at http://pubs.acs.org.

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