Amination of Nitrobenzene via Nucleophilic Aromatic Substitution for Hydrogen: Direct Formation of Aromatic Amide Bonds

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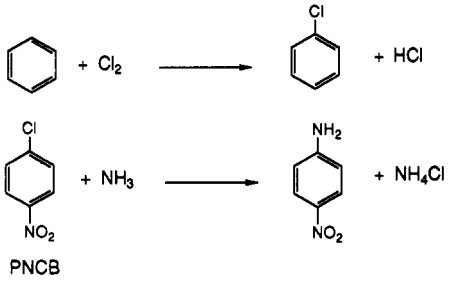
The first example of the direct formation of aromatic amide bonds via nucleophilic aromatic substitution for hydrogen is described. Thus, the reaction of benzamide, tetramethylammonium hydroxide dihydrate, and nitrobenzene under anaerobic conditions generates *N*-(4-nitrophenyl)-benzamide (1) (98%) and azoxybenzene (30%) in isolated yields. In addition, other substituted benzamides and aliphatic amides are shown to function as nucleophiles in this reaction. A mechanism that is consistent with the simultaneous formation of anilide products and azoxybenzene which requires the oxidation of σ-complex intermediates by nitrobenzene initially generating nitrobenzene radical anions is proposed. By contrast, when the reaction is run under aerobic conditions, the formation of azoxybenzene is completely inhibited due to the trapping of nitroarene radicals by O_2. The ability to prepare 1 in high yield and regioselectivity affords a novel route for the direct amination of nitrobenzene that does not require halogenated intermediates or auxiliary leaving groups. Accordingly, treatment of 1 with methanolic ammonia results in the aminolysis of the amide bond producing 4-nitroaniline and regenerates benzamide.

A variety of methods allow for the addition of nucleophiles to nitroarenes.[1] With respect to synthetic utility, nucleophilic aromatic substitution for halide has long been the procedure of choice. Indeed, one of the oldest practiced industrial chemical reactions is the activation of aromatic C–H bonds by chlorine oxidation. The resulting chlorobenzenes can be further activated by nitration to give a mixture of *o*- and *p*-nitrochlorobenzenes (PNCB) which are used in the manufacturing of aromatic amines. Thus, when these intermediates are reacted with ammonia, the corresponding nitroanilines are produced. Since neither



PNCB

chlorine atom ultimately resides in the final product when this chemistry is employed, the ratio of pounds of byproducts produced per pound of product generated is highly unfavorable. In addition, these processes typically generate aqueous waste streams which contain high levels of inorganic salts contaminated with organics which are difficult and expensive to treat. A similar situation exists for the commercial production of materials which contain aromatic amide bonds. For instance, aromatic polyamides are typically generated via the reaction of aromatic amines and diacid chlorides.[2] In addition, there are numerous examples of aromatic amide bond formation by the reaction of isocyanates (produced by phosgenation, Cl_2-CO) and aromatic carboxylic acids.[3]

Several different methods for the direct amination of nitrobenzene that do not require chlorobenzenes have been reported. The most useful of these with respect to synthetic utility is vicarious nucleophilic substitution for hydrogen (VNS).[4] This class of reaction has been shown to be useful for the introduction of carbon, oxygen, and amine nucleophiles into nitroarenes but demands the positioning of a good leaving group α to the nucleophilic center which is eliminated during the decomposition of the proposed σ-complex intermediate.[5] Two relevant examples of VNS reactions are the amination of nitrobenzene with 4-amino-1,2,4-triazole,[5g,h] or, more recently, with sulfenamides.[5f] These methods generate reasonable yields of nitroanilines, 58% and 85%, respectively, with the latter giving a 5:1 mixture the *para* and *ortho* isomers. While these reactions do not use halogenated materials as the primary reagents, the requirement of the auxiliary leaving group demands a means of regenerating the original aminating agent. In the case of sulfenamides, this is accomplished by a NaOCl oxidation which introduces chlorides into the system.

By contrast, a more direct and atomically efficient route for the production aromatic amines and amides would be via the direct displacement of hydrogen from nitrobenzene using amides as nucleophiles. Aminolysis of the resulting aromatic amide bond would produce the corresponding nitroaniline. The direct amination of nitrobenzene via

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nucleophilic aromatic substitution for hydrogen (NASH) reactions has been reported.[6] For instance, the reaction of nitrobenzene with sodamide in liquid ammonia[7] or lithium amide in refluxing nitrobenzene[8] was shown to produce complex mixtures of nitroanilines in no greater than 5% overall yield. In addition, the patent literature claims the amination of ntirobenzene via a variety of acid/metal-catalyzed processes.[9] However, these reactions proceed in low yields and utilize halogenated materials.

We have recently described a NASH reaction between aniline and nitrobenzene which produces the corresponding *para*-substituted diphenylamines in high yields.[10] We now report the extension of this chemistry to amide nucleophiles. Accordingly, in this report we describe the first example of the direct formation of aromatic amide bonds via NASH chemistry. This reaction is unique in that it generates exclusively the *para*-substituted anilide derivatives in high yield under mild conditions using either nitrobenzene or O_2 as the terminal oxidant. Furthermore, this reaction forms the basis of a new route for the production of *p*-nitroanilines and its derivatives that does not require the use of halogenated oxidants or intermediates.

Results

The addition of tetramethylammonium hydroxide dihydrate (TMA(OH)·$2H_2O$, 0.01 mol) to a solution of benzamide (0.01 mol) in nitrobenzene (10 mL) under anaerobic conditions at 80 °C causes the formation of a dark red solution. The mixture was subjected to vacuum distillation for 1 h at 80 °C to remove water. Subsequent analysis of the reaction by reverse phase HPLC revealed that all of the benzamide was consumed, generating *N*-(4-nitrophenyl)benzamide (1) in quantitative yield. The only other observable products were water and azoxybenzene (2), which was formed in 33% yield based on benzamide (Figure 1A). Analysis of the reaction mixture by EPR spectroscopy revealed that nitrobenzene radical anion was also formed during the course of the reaction, as is evident by its distinct 54-line pattern.[11] UV/vis spectrophotometry of the final reaction mixture showed an absorbance with λ_{max} = 466 nm, which was identical to the spectrum generated by the addition of TMA(OH)·$2H_2O$ to a DMSO solution of 1.[12] This indicates that the primary product of this reaction was the tetramethylammonium salt of *N*-(4-nitrophenyl)benzamide (3). Isolation of 3 in 98% yield was achieved by precipitation from the reaction with hexanes. Subsequent acidification of an aqueous solution of 3 generates 1 quantitatively. Substituted benzamides as well as aliphatic amides can also function as nucleophiles in this reaction, producing the corresponding anilide derivatives in excellent yields (Table I).

The amount of water present in the reaction mixture has a dramatic effect on the yield of anilide products. Thus, as the mole ratio of water to base is increased, the yield of 1 decreases substantially (Table II). Consistent with this result is the observation that if water is not contin-

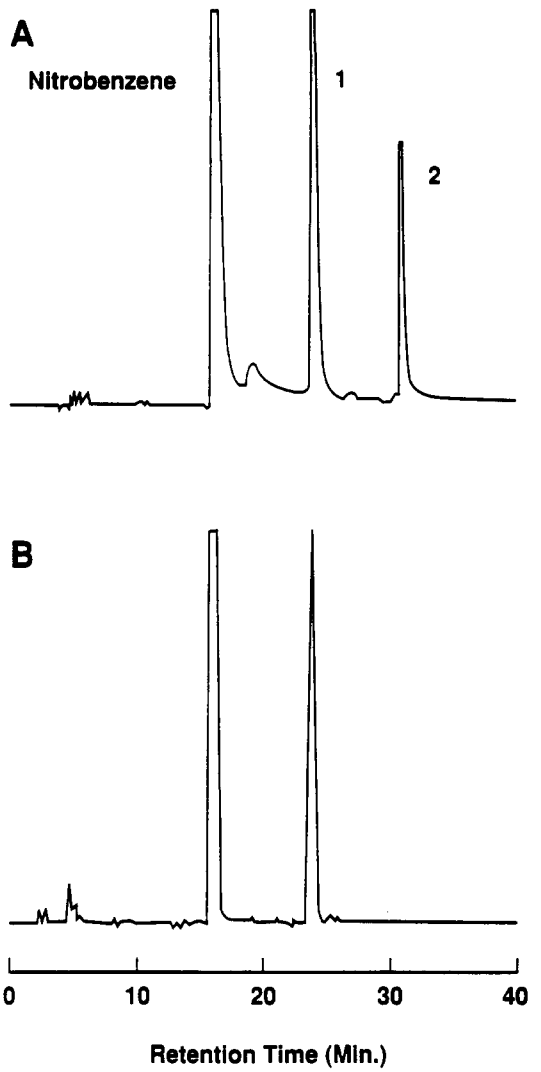

Figure 1. Reverse phase HPLC chromatograms of the completed reaction of benzamide and nitrobenzene under (A) anerobic conditions and (B) aerobic conditions.

Table I. Yields of *N*-(4-Nitrophenyl)amides

amide	% yield[a] 4-nitrobenzanilide derivative
benzamide	98
4-nitrobenzamide	95
4-chlorobenzamide	95
4-methylbenzamide	95
4-methoxybenzamide	95
isobutyramide	75 (93)[b]

[a] Isolated yields based on moles of amide charged. [b] HPLC yield.

Table II. Effect of Water on the Yield of *N*-(4-Nitrophenyl)benzamide (3)

molar ratio of water: TMA(H)	% yield[a] of 3
10	0
7	0
3	5
1	77

[a] Yields are based on moles of benzamide charged and were determined by reverse phase HPLC analysis as described in the Experimental Section.

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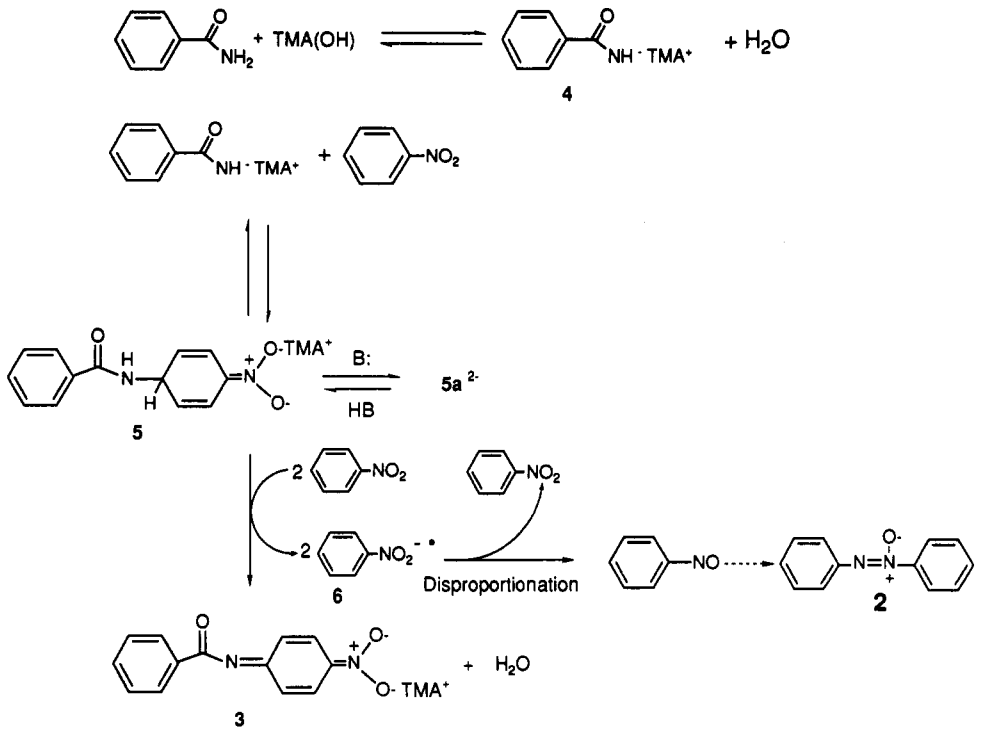
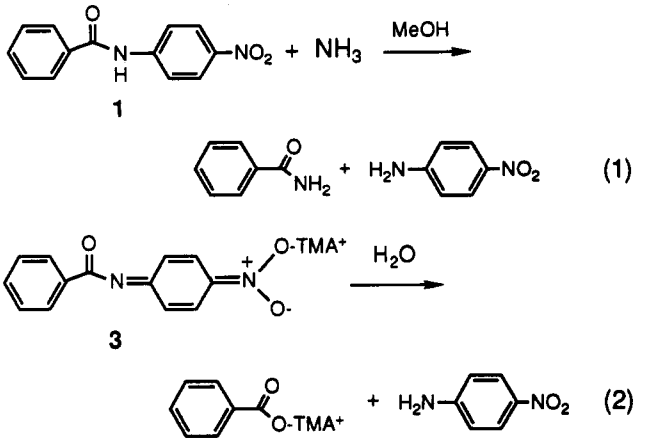


Figure 2.

uously removed from the reaction by distillation, **3** forms in only 40% yield. It is interesting to note that a similar water effect was observed when aniline was used as the nucleophile and most likely reflects the requirement for deprotonation of the amines to increase their nucleophilicity.[10]

It was possible to prepare **1** in the absence of **2** by conducting the reaction under aerobic conditions. Accordingly, benzamide and tetramethylammonium hydroxide dihydrate were reacted in nitrobenzene under a constant air purge to simultaneously introduce O_2 and remove water. Analysis of the reaction mixture by reverse phase HPLC showed **2** as the only detectable product in 93% yield (Figure 1B). Under these conditions azoxybenzene production was completely inhibited. In addition, an EPR spectrum of the reaction mixture was devoid of a signal indicating that nitrobenzene radical anion was not generated under these conditions. If this reaction was conducted under O_2 pressure without removal of water, **1** was generated in only 20% yield.

The treatment of **1** with methanolic ammonia at 120 °C results in the aminolysis of the amide bond, producing 4-nitroaniline and regenerating the benzamide nucleophile (eq 1). It was also possible to produce 4-nitroaniline directly from **3** by the addition of water to the final reaction mixture at 70 °C. Under these conditions the amide bond is readily hydrolyzed (Eq 2).



Discussion

The substitution of hydride in the reaction or nucleophiles with nitrobenzene can formally be viewed as the removal of a proton and two electrons from a σ-complex intermediate. Since hydride is a poor leaving group, this oxidation is often facilitated by the addition of an external oxidant[1] or in many cases by the nitroaromatic itself.[10,13] The fact that azoxybenzene is observed as a byproduct of this reaction under anaerobic conditions and that the distinct EPR spectrum of nitrobenzene radical anion is observed in the reaction mixtures indicate that nitrobenzene is functioning as the primary oxidant in this system. A similar product profile was observed in the reactions of silyl enol ethers and nitrobenzene to give *o*- and *p*-nitroaryl carbonyl compounds.[14] In the absence of an external oxidant, the corresponding azoxybenzene derivative was formed via reduction of nitrobenzene. However, when Br_2 or DDQ was added, no azoxybenzene byproduct was observed due to the rapid oxidation of the σ-complex intermediate by these materials.

A general mechanism consistent with the observed water effect, the detection of nitrobenzene radical anion, and the simultaneous formation of **2** and **3** is shown in Figure 2. Deprotonation of benzamide generates the benzanilide

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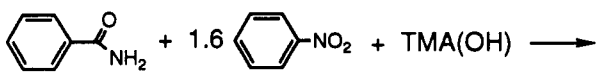
anion 4 and water. Subsequent attack of 4 at the *para* position of nitrobenzene generates the expected σ-complex intermediate 5.[15] Intermolecular oxidation of 5 by nitrobenzene generates 3 and initially nitrobenzene radical anion 6 which can decompose by a variety of pathways including disproportionation to give nitrosobenzene.[16] The ultimate formation of azoxybenzene is then governed by a cascade of electron transfer and nucleophilic reactions between the radical anions of nitrobenzene, nitrosobenzene, and *N*-hydroxyaniline, all of which can be directly accessed in the reaction mixture by the reduction of nitrobenzene to various extents.[17] The overall stoichiometry required by this mechanism (eq 3) is consistent with the observed yields of 2 and 3.



$$3 + 0.33\ 2 + 2\,H_2O \quad (3)$$

We have reported a similar mechanism for the formation of (4-nitrosophenyl)- or (4-nitrophenyl)-phenylamine from the reaction of aniline and nitrobenzene.[10] In that reaction, both an intramolecular and intermolecular oxidation pathway were operative, the partitioning of which could be controlled by the initial ratio of aniline to nitrobenzene. Intramolecular oxidation was favored when nitrobenzene concentrations were low and intermolecular oxidation was preferred when nitrobenzene concentrations were high. By contrast, in the case of benzamide, *N*-(4-nitrosophenyl)-benzamide was not observed as a reaction product even when a large excess of benzamide was used, conditions which favor the intramolecular oxidation pathway in the case of aniline. It is also interesting to note that no *ortho* substitution products are observed in the reactions of the amides with nitrobenzene. It is known that the more sterically demanding nucleophiles generally prefer attack at the less hindered *para* position despite the increased electrophilicity of the α-carbon.[1] Yet, even when *tert*-butoxide is used as a nucleophile, products resulting from *ortho* attack are observed.[18] One possible explanation for the unusually high *para* selectivity associated with amide nucleophiles is that the tetramethylammonium salt of the anilide species, the ultimate product of this reaction, is required to adopt a quinodiimine structure. This may force a unfavorable steric interaction between the carbonyl oxygen atom and the nitro group destabilizing the *ortho* product with respect to the corresponding *para* isomer. Thus, while attack at the *ortho* position might be kinetically favored, the oxidation to products might be expected

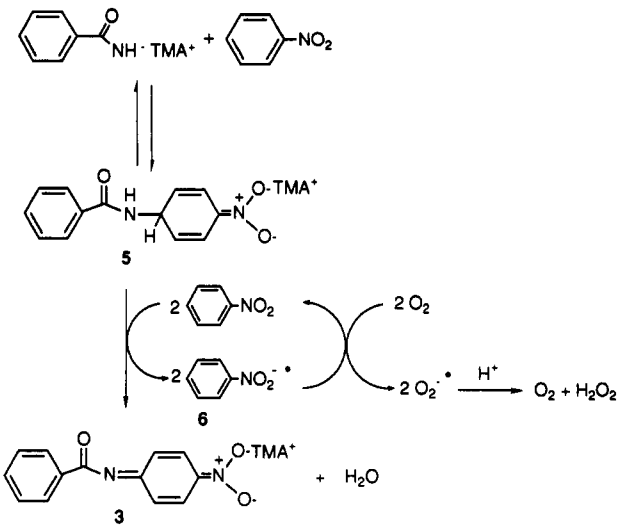


Figure 3.

to be unfavorable and slower than the oxidation of the corresponding *para* adduct.

The direct formation of nitrobenzene radical anions by oxidation of σ-complex intermediates has been observed in other examples of NASH reactions. For instance, Guthrie and Nutter detected significant quantities of nitrobenzene radical anion in the reaction of *tert*-butoxide and nitrobenzene in THF.[18] They proposed a mechanism where 2 mol of nitrobenzene oxidize the corresponding dianion of a σ-complex intermediate via two sequential electron-transfer steps. In the reactions reported here, we cannot rule out the intermediacy of a dianion intermediate, **5a**, generated by the deprotonation of **5**. However, in the case of amide nucleophiles, it is not clear whether deprotonation would occur at the *para* carbon or on the amide nitrogen, making an unambiguous structural assignment of such an intermediate and its requirement in the oxidation mechanism speculative at this time.[19]

The mechanism outlined in Figure 2 proposes the intermediacy of a nitrobenzene radical anion as the first species generated by the oxidation of **5**. It was our contention that since nitrobenzene radical anions are indeed generated by the oxidation of **5**, and are ultimately responsible for the formation of the azoxybenzene byproduct, trapping these species should inhibit the production of azoxybenzene without significantly affecting the production of **3**. We chose dioxygen as the radical trap since O_2 is known to readily oxidize nitrobenzene radical anions[16a,18,20] and is both an economically and environmentally favorable oxidant.

A unified mechanism for the production of **3** under aerobic conditions that is consistent with all of the experimental observations is shown in Figure 3. Nitrobenzene oxidation of σ-complex intermediate **5** or **5a** generates the nitrobenzene radical anion **6**. However, under aerobic conditions **6** is readily trapped by O_2, generating superoxide and nitrobenzene.[19] Superoxide anion would be expected to dismutate under these reaction

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(19) We have found that the pK_a of both the aniline and amide nucleophiles as well as the concentration of hydroxide has a profound effect on whether these reactions will proceed via an inter- or intramolecular oxidation pathway. These observations suggest that dianion intermediates may be involved in the oxidation step.

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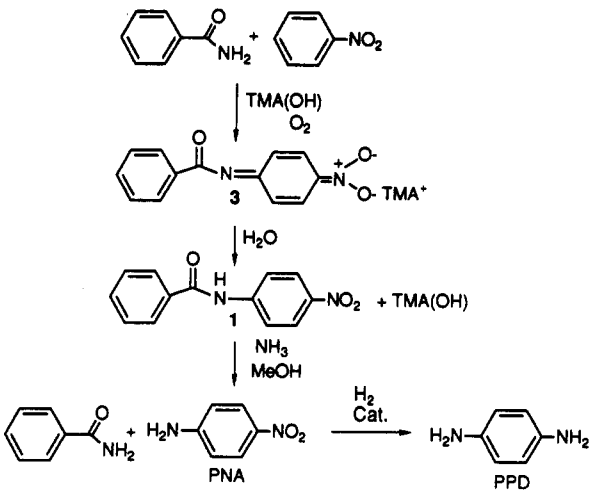

Figure 4.

conditions to produce O_2 and H_2O_2.[21] It is not clear at this time whether H_2O_2 further contributes in the production of **3** by direct oxidation of **5**. We conclude that the aerobic reaction pathway inhibits the formation of azoxybenzene by the rapid reaction between O_2 and **6**, diverting the electron-transfer cascade. In support of this mechanism is the fact that no EPR signal was observed when the reaction was conducted under aerobic conditions. As a result of the facile reaction between O_2 and **6**, dioxygen is ultimately used as the terminal oxidant in this system. Thus, in contrast to the aerobic reaction of aniline and nitrobenzene which produces large quantities of azobenzene, the oxidative coupling of amides with nitrobenzene is greatly improved by utilizing dioxygen since the nucleophile is resistant to autoxidation.[22]

The ability to prepare **1** and **3** in high yield and regioselectivity affords a novel route for the preparation of 4-nitroaniline (PNA) and its derivative *p*-phenylenediamine (PPD) (Figure 4). The addition of water to **3** causes protonation of the amide nitrogen, producing **1** and regenerating TMA(OH). Subsequent reaction of **1** with ammonia causes the direct cleavage of the amide bond, generating PNA which can be hydrogenated to PPD under catalytic conditions. It is important to note that this route is both catalytic in TMA(OH) and also allows for the recycling of the amide nucleophile. *Accordingly, the overall stoichiometry for this series of reactions illustrates the formal amination of nitrobenzene with ammonia.*

In conclusion, the formation of substituted anilides from the reaction of amides with nitrobenzene is the first example of the direct formation of aromatic amide bonds via nucleophilic aromatic substitution for hydrogen and represents a new route for the amination of nitrobenzene. This reaction proceeds in high yield and regioselectivity and does not require the use of halogenated materials or auxiliary leaving groups. Furthermore, our studies have demonstrated that the use of O_2 as the terminal oxidant in NASH reactions can result in highly selective and environmentally favorable routes for the production of commercially relevant aromatic amines.

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(22) The reaction of aniline and nitrobenzene under aerobic conditions produces large quantities of azobenzene. Under these conditions azobenzene is produced by the oxidative coupling of two anilines via a pathway that is independent from the oxidation of σ-complex intermediates. See: (a) Wohl, A. *Chem. Ber.* **1903**, *36*, 4135. (b) Jeon, S.; Sawyer, D. T. *Inorg. Chem.* **1990**, *29*, 4692.

Experimental Section

General Procedures. Reactions were monitored by reverse phase HPLC using the external standard method. A Waters 600 series HPLC equipped with a Vydac 201HS54 (4.6 × 250 mm) column and UV detection at 254 nm were employed in all the analyses. Elution gradient: initial conditions = 75% A and 25% B, flow rate 1.5 mL/min; 0–35 min, 20% A and 80% B; 35–40 min, 100% B; 40–45 min, 100% B. Solvent A = water, solvent B = 40% methanol in acetonitrile. ^{1}H-NMR spectra were obtained on a Varian VXR-300 spectrometer. Mass spectral analyses were carried out by electron impact (EI) and methane chemical ionization (CI-CH_4) on a Finnigan 4500 system equipped with a Teknivent Two data system by both. Nitrobenzene, benzamide, 4-nitrobenzamide, 4-chlorobenzamide, 4-methylbenzamide, and 4-methoxybenzamide were purchased from Aldrich Chemical Co. and were used without further purification. Tetramethylammonium hydroxide pentahydrate (Aldrich) was converted to the dihydrate by lyophilization overnight. The extent of hydration of the resulting salt was determined by standard titration techniques.

Authentic samples of the disubstituted benzanilides were prepared by the reaction of the 4-nitroaniline with the appropriately substituted benzoyl chloride. Thus, in a typical example, a solution containing 10 mmol of 4-nitroaniline and 10 mmol of 4-methylbenzoyl chloride in 50 mL of toluene was stirred at reflux for 12 h. After the solution was cooled to ambient temperature, the resulting product was filtered and washed with hexane. The precipitate was air dried and 4-methyl-*N*-(4-nitrophenyl)benzamide was obtained in 90% yield. All of the substituted benzanilides produced by this method gave the appropriate MS analysis and were analytically pure by reverse phase HPLC analysis. The retention time of the standards made in this manner using the HPLC conditions described above are as follows: *n*-(4-nitrophenyl)benzamide, 25.6 min; 4-methoxy-*N*-(4-nitrophenyl)-benzamide, 26.8 min; 4-chloro-*N*-(4-nitrophenyl)benzamide, 30.8 min; 4-methyl-*N*-(4-nitrophenyl)benzamide, 28.3 min; 4-nitro-*N*-(4-nitrophenyl)benzamide, 29.2 min.

Preparation of *N*-(4-Nitrophenyl)benzamide under Anaerobic Conditions. A solution of 10 mmol of benzamide and 10 mmol of tetramethylammonium hydroxide dihydrate in 10 g of nitrobenzene was stirred under vacuum (40 mmHg absolute) at 65 °C for 1 h. During this time nitrobenzene and water were being distilled from the reaction. After the solution was cooled to ambient temperature, 5 mL of anhydrous DMSO was added to homogenize the solution. An aliquot was analyzed by reverse phase-HPLC by an external standard method. The HPLC yield of *N*-(4-nitrophenyl)benzamide was 100% and 33% of azoxybenzene was produced. Hexane (50 mL) was then added to the reaction mixture, causing the immediate precipitation of the tetramethylammonium salt of *N*-(4-nitrophenyl)benzamide as a brown solid. The crude product was washed with warm toluene (under 80 °C) to remove excess nitrobenzene and air dried, giving a 98% yield *N*-(4-nitrophenyl)benzamide tetramethylammonium salt: ^{1}H NMR (DMSO-d_6) δ 8.1 (d, 2H), 8.0 (d, 2H), 7.75 (d, 2H), 7.4 (m, 3H), 3.1 (s, 12H). The filtrate was evaporated to dryness and chromatographed over silica with 10% ethyl acetate/90% hexane to obtain a 30% yield of azoxybenzene based on benzamide. The azoxybenzene isolated was compared with an authentic sample by reverse phase HPLC and MS.

N-(4-Nitrophenyl)benzamide was isolated as the free amine by dissolving the salt in 200 mL of water which was then acidified with 1.5 equiv of acetic acid. A light brown precipitate formed which was filtered and air dried. The product was recrystallized from toluene or 50% hexane/50% ethyl acetate solution to obtain an analytically pure sample which gave a single peak at 25.6 min on reverse phase HPLC: MS-EI m/z = 242.

Preparation of Disubstituted Benzanilides. A solution containing 10 mmol of substituted benzamide and 1.5 equiv of tetramethylammonium hydroxide dihydrate was stirred in 10 mL of nitrobenzene under vacuum (40 mmHg absolute) at 70 °C for 4 h. During this time, nitrobenzene and water were removed

from the reaction by distillation. The reaction solution was cooled and the corresponding disubstituted benzanilides were isolated as the free amide in an identical fashion as described above. The benzanilides were characterized by mass spectral analysis and all gave single peaks on reverse phase HPLC at retention times identical to those of authentic samples prepared via the acid chloride method described above.

Preparation of *N*-(4-Nitrophenyl)benzamide under Aerobic Conditions. Benzamide (0.2 mol) and tetramethylammonium dihydrate (0.2 mol) were stirred in 100 mL of nitrobenzene at 65 °C with air sweeping the surface of the reaction solution for 8 h. Approximately 5 mL of water and 40 mL of nitrobenzene were collected in a Dean–Stark trap during this time. Another 100 mL of nitrobenzene was added and the solution was allowed to stir overnight. A total of 70 mL of nitrobenzene was collected. The solution was cooled to ambient temperature and then 100 mL of water was added with good stirring. The solution was filtered and the precipitate was washed with more water and dried under suction to obtain a dark brown solid. The solid was washed with hot hexane to obtain 43.5 g (90%) of *N*-(4-nitrophenyl)benzamide as a light brown solid.

Generating of *p*-Nitroaniline from *N*-(4-Nitrophenyl)-benzamide via Aminolysis. A solution of 100 mg of 4-nitrobenzanilide, 10 mL of liquid ammonia, and 50 mL of methanol was stirred in a steel pressure reactor at 120 °C for 12 h. The reaction was cooled to room temperature and the reactor was slowly vented. The reaction mixture was analyzed by reverse phase HPLC. 4-Nitroaniline and benzamide were produced in 50% yield based on *N*-(4-nitrophenyl)benzamide charged. The remaining 50% of *N*-(4-nitrophenyl)benzamide was unreacted.

Generation of *p*-nitroaniline from *N*-(4-Nitrophenyl)-benzamide via Hydrolysis. A solution of 10 mmol of benzamide and 10 mmol of tetramethylammonium hydroxide dihydrate in 10 g of nitrobenzene was stirred under vacuum at 65 °C for 1 h as described above. Water (50 mL) was added and the solution was stirred for an additional hour at 70 °C. The organic layer of the two-phase mixture was analyzed by reverse phase HPLC. 4-Nitroaniline was generated in 90% yield.

Benzamide Coupling Reaction with Various Amounts of Water. A 100-mL round-bottom flask equipped with an addition funnel and Dean–Stark trap was charged with benzamide (1.27 g, 10.4 mmol), TMA(H)·5H_2O (2.17 g, 11.9 mmol), and xylene (8.5 g). The xylene and water were removed by vacuum distillation (20 Torr). The reaction mixture was maintained between 70 and 80 °C and various amounts of water were then added back to the reaction. Following the re-addition of water, a mixture on nitrobenzene (1.23 g, 10.0 mmol) and DMSO (1.28 g) was added dropwise to the reaction under nitrogen over 30 min. The reaction was maintained at 80 °C and the mixture was allowed to stir. After 4 h an aliquot was removed and analyzed by HPLC.

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