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The Use of Formamidine Protection for the Derivatization of Aminobenzoic Acids

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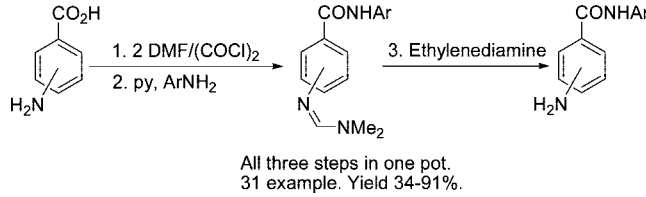

N,*N*-Dimethylformamidine and novel *N*,*N*-diisopropylformamidine protecting groups were used to carry out a one-pot conversion of aminobenzoic acids into the corresponding amides. General conditions for an in situ transformation of aminobenzoic acids and their heterocyclic analogues into the corresponding formamidine-protected acid chlorides were developed. These chlorides were used in reactions with amines, including poorly reactive anilines. The protected amides were then smoothly deprotected by heating with ethylenediamine derivatives, resulting in a general procedure for the one-pot transformation of aminobenzoic acids into their amides. Our one-pot procedure was successfully applied to the preparation of several compounds of pharmaceutical interest.

Introduction

There are numerous examples of anilides of 3- and 4-aminobenzoic acids and their heterocyclic analogues serving as key moieties or precursors to biologically active compounds. Oligomers of 2-aminopyrrole-3-carboxamide, such as netropsin, distamycin A, tallimustine, and brostallicin, as well as their aromatic congeners, are DNA minor groove binders and topoisomerase inhibitors, and they have been extensively studied as potential treatments for cancer and bacterial and viral infections.[1] The 3-aminobenzanilide suramin has been used clinically as a sensitizer to cancer chemotherapy and antiparasitic agent,[2] and some of its derivatives were reported to be selective P2X or P2Y,[3] and sirtuin[4] inhibitors. Other 3-aminobenzanilides were found to be potent bradykinin B_2 receptor antagonists,[5] as well as inhibitors of epidermal growth factor receptor,[6] DNA methyltransferase,[7] and cyclooxygenase-1.[8] Examples of biologically active 4-aminobenzanilides are the antimitotic agent DW2282,[9] ameltolide and other anticonvulsants,[10] antiviral compounds,[11] histone deacetylase inhibitor CI-994,[12] adenosine 2A receptor antagonists,[13] and vasopressin receptor antagonists lixivaptan, conivaptan, and mozavaptan.[14]

The aliphatic amides of aminobenzoic acids can be prepared under typical amide coupling conditions by taking advantage of the fact that the reactivity of aliphatic amines is much greater

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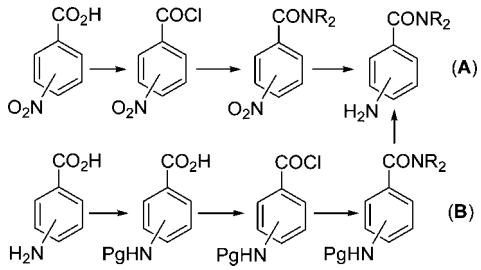
SCHEME 1. Literature Preparations of Aminobenzanilides



than the reactivity of the aromatic amine moiety of aminobenzoic acids.[15,16] However, the direct formation of aromatic amides from 3- and 4-aminobenzoic acids has been problematic, due to the cross-reactivity of their amine functionality.[6b,13] These amides are usually prepared in three steps starting with the corresponding nitrobenzoic acid. The nitro group is reduced in the final step (Scheme 1A).[5,7,8,10d,13,17] In cases when groups sensitive to reductive conditions are present, or the corresponding nitrobenzoic acids are not available, a four-step procedure involving protection and deprotection of the amino group must be applied (Scheme 1B).[1h,6b,7,17b,18]

When one has to prepare a series of many anilides of aminobenzoic acids, the three- and four-step sequences depicted in Scheme 1, albeit trivial, become inconvenient. Instead, we envisioned a method to streamline this sequence, in which the carboxylic group of the aminobenzoic acid is activated simultaneously with the protection of the amine group. Furthermore, we planned to react the resulting acid chloride with an aromatic amine and then to remove the labile protecting group in the same pot. To be useful, we required this procedure to be applicable to a wide range of both aromatic amines and aminobenzoic acids.

Results and Discussion

It did not escape our notice that the same conditions, involving the intermediacy of a Vilsmeier reagent (e.g., DMF/$POCl_3$), are used in the literature for the conversion of both carboxylic acids into acid chlorides[19] and primary arylamines into *N*,*N*-dimethylformamidines.[20] The *N*,*N*-dimethylformamidine moiety is a known protecting group for amines, which can be cleaved under mild conditions.[21] It has been used as an ortho-directing group in metal−halogen exchange reactions[22] as well as for the protection of amino-groups in heterocycles, particularly nucleotides, nucleosides, and their analogues.[23]

There are scattered references in the early patent literature to the preparation of *N*,*N*-dimethylformamidine-*N*′-benzoic acids using the Vilsmeier reagent, for example, from 3-amino-2,4,6-triiodobenzoic[24] or 4-aminobenzoic[20f] acids. However, in these publications, the formamidine-substituted benzoic acids were the final products and were not further derivatized or deprotected.

The reaction of 4-aminobenzoic acid (**1a**) and 4-methylaniline (**3a**) was chosen as a model system (Scheme 2). We found that adding **1a** at room temperature to a suspension of 2 equiv of the Vilsmeier reagent in CH_2Cl_2, prepared in situ from DMF and oxalyl chloride, directly provided the unstable acid chloride **2**. When **2** was further treated with 4-methylaniline (**3a**) and *N*,*N*-diisopropylethylamine (DIPEA), the protected amide **4** was produced in 76% isolated yield.

Using **4**, we screened several reagents known to remove the *N*,*N*-dimethylformamidine group (zinc chloride,[25] HCl,[26] NaOH,[23d] and ammonium hydroxide[23b,27]). In addition, we tried ethylenediamine, which has the advantage of higher nucleophilicity[28] than sodium hydroxide or ammonia. Although another

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SCHEME 2. Development of Formamidine Protection and Deprotection

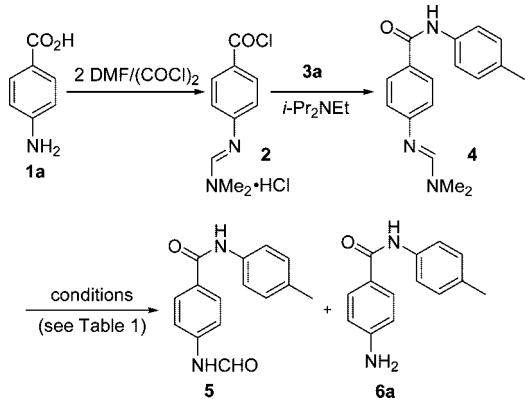

TABLE 1. Exploration of Deprotection Conditions[a]

entry	reagent	**4**[b] (%)	**5**[b] (%)	**6a**[b] (%)
1	$ZnCl_2$	1	53	46
2	4 M aq HCl	81	0	15
3	4.5 M aq NaOH	30	1	68
4	14.8 M aq NH_3	71	21	21
5	ethylenediamine	0	5	94

[a] 0.5 mmol of in **4** mL of EtOH was heated with 2.25 mmol of the deprotecting reagent at 80 °C in a sealed tube for 4 h. [b] Amount in the reaction mixture was determined by HPLC area method analysis.

primary amine, cyclohexylamine, was used in the literature,[23b] we chose to utilize ethylenediamine, as we envisioned its unlimited aqueous solubility to be advantageous during the workup. As expected, ethylenediamine gave the fastest and the cleanest deprotection, while significant amounts of unreacted **4** and formamide **5** were present in all other cases (Table 1). We were pleased to find that after the deprotection with ethylenediamine, an 80% isolated yield of **6a** was obtained.

With the conditions for the separate steps established, we moved toward our main goal of carrying out the synthesis in one pot without isolating intermediate **4**. Thus, upon completion of the formation of **4** as judged by HPLC analysis, we replaced the CH_2Cl_2 solvent with ethanol and heated the resulting solution with ethylenediamine. To our satisfaction, with all three steps carried out in the same pot, an overall 88% isolated yield of amide **6a** was obtained from **1a** (Table 2, entry 1).

Unexpectedly, when we tried to apply the above procedure to the reaction of **1a** with 4-nitroaniline, a mixture of products was formed. However, the simple replacement of the DIPEA base with pyridine in the amide bond formation step resulted in 88% overall yield of the desired product **6b** (entry 2). We speculate that DIPEA, being a strong base, converts **2** to the free-base form, thus promoting the side reaction of self-acylation on the amidine nitrogen.[29] This competing reaction occurring in the presence of DIPEA is, probably, much slower than the amide formation in the case of the rapidly reacting 4-methylaniline (entry 1). However, the self-acylation side reaction in the presence of DIPEA becomes predominant in the case of deactivated 4-nitroaniline. To avoid this complication, we used pyridine as the base in all subsequent reactions. After this final optimization, we set out to explore the substrate scope of the method by varying both the acid (**1**) and amine (**3**) components (Table 2). We placed a particular emphasis on the most challenging substrates—anilines with low nucleophilicity—using 4-nitroaniline[30] and 2,6-dichloroaniline as primary examples.

The method worked equally well for the reactions of 4-aminobenzoic acid with electron-poor 4-nitroaniline (entry 2), electron-rich 4-methoxyaniline (entry 3), and the aliphatic amine pyrrolidine (entry 4). High yields were also obtained starting with 3-aminobenzoic acid (entries 8 and 9). 2,6-Dichloroaniline afforded somewhat lower but still good yields (entries 5 and 10).

Importantly, the described method was fully applicable to heterocyclic 6-aminonicotinic acid (entries 11−14). As noted in the introduction (also compare with Scheme 1B), our approach brings the greatest benefit when the nitrobenzoic acid corresponding to the aminobenzoic acid cannot be used. In the case of 6-aminonicotinic acid, 6-nitronicotinic acid is commercially available but more than ten times more expensive. Underscoring the advantage over existing procedures, the following examples demonstrate the use of other aminobenzoic acids with the price ratio of nitro/amino > 10: 2-aminopyridin-4-ylcarboxylic (entry 15), 3-amino-1,2,4-triazol-5-ylcarboxylic (entries 16 and 17), and 4-amino-2-hydroxybenzoic (entry 18) acids. Even greater benefit is achieved when the corresponding nitrobenzoic acids are not commercially available as in the case of 4-amino-3,5-dichlorobenzoic (entries 19 and 20) and 4-amino-3-chloro-6-methoxybenzoic (entry 21) acids.

The preparation of 4-nitroanilides (entries 2, 9, 12, 16, 19, 22, and 24) and amides of benzoic acids containing both amino- and nitro-groups (entries 22−25) highlights another important feature of our method—its applicability to substrates containing reduction-sensitive functional groups. For these compounds, the classical synthesis from nitrobenzoic acids (Scheme 1A) would require developing chemoselective reduction methods,[31] while our approach avoids this inconvenience.

While all other amines afforded high yields, the reactions involving 2,6-dichloroaniline were generally less efficient and required longer time. The lower yields could be remedied by using 2 equiv of 2,6-dichloroaniline (see entries 14, 17, and 20, values in parentheses).

For the benzoic acids with the deactivated amino group, such as 6-aminonicotinic and 3,5-dichloro-6-aminobenzoic acids, addition of pyridine, followed by stirring at room temperature *prior to* the addition of the aniline, was necessary for the protection to be complete. For other acids (e.g., 4-aminobenzoic), the order of addition did not matter. In most cases, we used the more general procedure, in which pyridine was added first. On the second step, the reaction time required to form the amide bond varied greatly depending on the reactivity of the amine, from 1 h for the reactive 4-methylaniline to 2−6 d for 2,6-dichloroaniline, and the addition of DMAP and heating were necessary for 4-aminopyridine (entry 27). The ease of the final deprotection step also depended on the individual reactivity of the substrates. The deprotection of the formamidine group positioned off the pyridine ring was complete within 30 min at reflux with ethylenediamine (entries 11−14), while the deprotection of dichlorophenyl derivatives (entries

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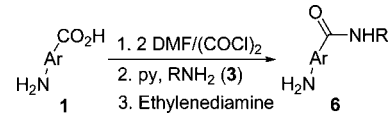
TABLE 2. One-Pot Synthesis of Aminobenzamides



entry	carboxylic acid (1)	amine (3)	product	yield (%)
1	4-aminobenzoic	4-methylaniline	**6a**	88[a]
2	4-aminobenzoic	4-nitroaniline	**6b**	88
3	4-aminobenzoic	4-methoxyaniline	**6c**	85
4	4-aminobenzoic	pyrrolidine	**6d**	91
5	4-aminobenzoic	2,6-dichloroaniline	**6e**	60
8	3-aminobenzoic	4-methylaniline	**6f**	82
9	3-aminobenzoic	4-nitroaniline	**6g**	89
10	3-aminobenzoic	2,6-dichloroaniline	**6h**	63
11	6-aminonicotinic	4-methylaniline	**6i**	91
12	6-aminonicotinic	4-nitroaniline	**6j**	83
13	6-aminonicotinic	pyrrolidine	**6k**	84
14	6-aminonicotinic	2,6-dichloroaniline	***6l***	48 (74%)[b]
15	2-aminopyridin-4-ylcarboxylic	2,6-dichloroaniline	**6m**	29
16	3-amino-1,2,4-triazol-5-ylcarboxylic (0.5H_2O)	4-nitroaniline	**6n**	50[c] (90)[b,c]
17	3-amino-1,2,4-triazol-5-ylcarboxylic (0.5H_2O)	2,6-dichloroaniline	**6o**	20[c] (34)[b,c]
18	4-amino-2-hydroxybenzoic	3-chloroaniline	**6p**	67
19	4-amino-3,5-dichlorobenzoic	4-nitroaniline	**6q**	87
20	4-amino-3,5-dichlorobenzoic	2,6-dichloroaniline	**6r**	33 (72)[b]
21	4-amino-3-chloro-6-methoxybenzoic	2-diethylaminoethylamine	**6s**	84[b]
22	5-amino-2-nitrobenzoic	4-nitroaniline	**6t**	87
23	5-amino-2-nitrobenzoic	2,6-dichloroaniline	**6u**	61
24	4-amino-3-nitrobenzoic	4-nitroaniline	**6v**	85
25	4-amino-3-nitrobenzoic	2,6-dichloroaniline	**6w**	59
26	4-amino-3-chlorobenzoic	2-aminothiazole	**6x**	42
27	3-aminobenzoic	4-aminopyridine	**6y**	64[d]
28	3-aminobenzoic	3-aminobenzoic acid	**6z**	87[e]

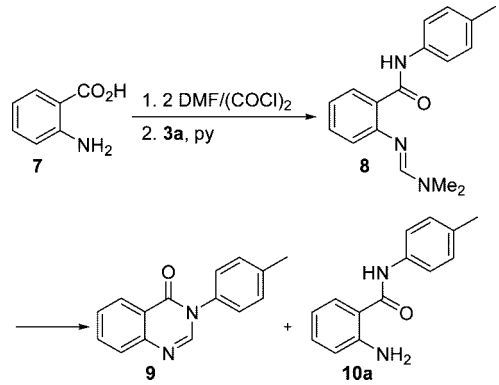
[a] DIPEA used in place of py. [b] 2 equiv of **3** was used. [c] 2.5 equiv of DMF/$COCl_2$ was used. [d] DMAP was added. [e] No base was used.

19 and 20) required several hours (see the Supporting Information for details).

We found our method to be convenient for the synthesis of several benzamides of pharmaceutical interest. For example, we used our protocol to obtain a reported potent epidermal growth factor receptor inhibitor[6b] (entry 18), adenosine 2A receptor ligand[13] (entry 26), antiemetic metoclopramide (entry 21), and bradykinin antagonist[5] (entry 27) in moderate to good yields. We also prepared the dimer of 3-aminobenzoic acid **6z** (entry 28), a core feature in several DNA-binding agents,[1d,f,g,j] using our one-pot procedure, while the classical method required two steps.[32] Interestingly, the use of pyridine in the synthesis of **6z** resulted in the formation of multiple products. The best yield of **6z** was obtained when *no base* was employed in the amide formation step, with DMF itself, possibly, acting as a base.[33]

Encouraged by the above results we decided to expand the scope of our method to 2-aminobenzoic acid. Although several direct methods for the preparation of 2-aminobenzanilides are known, for example, via isatoic anhydride[34] or from the acid itself utilizing thionyl chloride,[35] the importance of these

SCHEME 3. Formation of Quinazolinone 9



derivatives as intermediates in the synthesis of quinazolines[36] warrants the development of other methods.

When we tried to apply our approach to the reaction of 2-aminobezoic acid and 4-methylaniline, the intermediate **8** formed in high yield (LC-MS analysis). However, this compound was unstable and cyclized to quinazolinone **9**, when the reaction mixture was left for 16 h at room temperature (Scheme 3). Attempts to deprotect **8** immediately after formation by heating it with ethylenediamine, other amines, or hydrochloric acid led to mixtures of **9** and the desired product **10a** in various ratios.

We envisioned that the most straightforward way to prevent the unwanted cyclization to **9** would be to create a steric

(32) Bredereck, H.; Schuh, H. *Chem. Ber.* **1948**, *81*, 215.

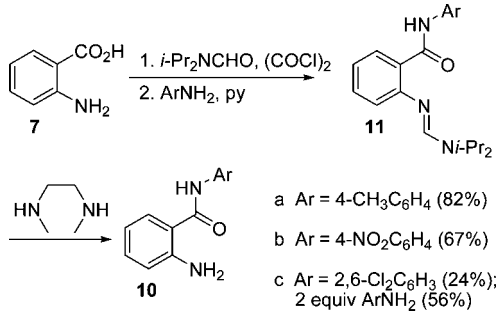
(33) DMF forms strong complexes with HCl having the composition DMF·HCl and DMF·2HCl, in both neat and 1,1,2,2-tetrachloroethane solutions: (a) Kislina, I. S.; Librovich, N. B.; Maiorov, V. D. *Russ. Chem. Bull.* **1994**, *43*, 1505. (b) Kislina, I. S.; Maiorov, V. D.; Sysoeva, S. G. *Russ. Chem. Bull.* **1997**, *46*, 916.

(34) For example, see: (a) Manhas, M. S.; Amin, S. G.; Rao, V. V. *Synthesis* **1977**, 309. (b) Kornet, M. *J. Heterocycl. Chem.* **1992**, *29*, 103.

(35) For example, see: (a) Garin, J.; Merino, P.; Orduna, J.; Tejero, T.; Uriel, S. *Tetrahedron Lett.* **1991**, *27*, 3263, and references cited therein. (b) Tani, J.; Yamada, Y.; Oine, T.; Ochiai, T.; Ishida, R.; Inoue, I. *J. Med. Chem.* **1979**, *22*, 95.

(36) (a) Armanego, W. L. F. *The Chemistry of Heterocyclic Compounds. Vol. 24. Fused Pyrimidines. Part I. Quinazolines*; Weissberger, A., Ed.; Wiley Interscience: New York, 1967, p. 87. (b) Brown, D. J. *The Chemistry of Heterocyclic Compounds. Vol. 55. Quinazolines, Suppl. I*; Taylor, E. C., Ed.; Wiley Interscience: New York, 1996, p. 31.

SCHEME 4. Preparation of Anthranylamides 10



hindrance around the amidine carbon by using a larger dialkylamino group. Using our general conditions, but replacing DMF in the protection−activation reaction with *N*,*N*-diisopropylformamide (Scheme 4), we obtained the *N*,*N*-diisopropylformamidine protected amide **11a** (LC-MS analysis). As expected, **11a** was stable and not prone to cyclization. However, the enhanced stability of **11a** was such that our standard deprotection method of heating with ethylenediamine in refluxing ethanol failed to remove the protecting group. Nevertheless, heating at a higher temperature with the more nucleophilic *N*,*N*′-dimethylethylenediamine accomplished the deprotection smoothly, affording **10a** in 82% isolated yield. To our satisfaction, this reaction also could be extended to poorly reactive 4-nitro- and 2,6-dichloroanilines to provide the corresponding amides **10b** and **10c**. In a manner similar to some other examples mentioned above, 2 equiv of 2,6-dichloroaniline was necessary to afford **10c** in a satisfactory yield (56%). We note that this yield was double the one reported in the literature (28%) for the conventional procedure depicted in Scheme 1A.[37] To the best of our knowledge, the described procedure is the first example of the use of *N*,*N*-diisopropylformamidine as a protecting group.

In summary, a method for the simultaneous protection and activation of aminobenzoic acids for amide formation has been developed. The transformation was effected by the reaction of aminobenzoic acids with excess Vilsmeier reagent, affording *N*,*N*-dimethylformamidine protected acid chlorides. These acid chlorides were used in situ for direct coupling reactions with amines, particularly, with weakly nucleophilic anilines to form the corresponding anilides. A novel method for the deprotection of the *N*,*N*-dimethylformamidine group with ethylenediamine was developed and applied to the resulting amides. The combination of the above steps resulted in a convenient one-pot synthesis of amides of aminobenzoic acids. For many substrates, we find this protocol to be superior to the classical 3−4 step methods in terms of speed, materials availability, and generality. The procedure was also successfully applied to several targets of pharmaceutical interest. A novel *N*,*N*-diisopropylformamidine protecting group was developed along the way, allowing the extension of the one-pot protocol to the preparation of amides of 2-aminobenzoic acid.

Experimental Section

Preparation of 4-((Dimethylamino)methyleneamino)-*N*-4-tolylbenzamide (4). The Vilsmeier reagent was prepared by adding oxalyl chloride (2.52 g, 19.8 mmol) dropwise to a solution of anhyd DMF (1.50 g, 20.5 mmol) in CH_2Cl_2 (20 mL) at 0−5 °C (Caution: Foaming!) with stirring at rt for 30 min. **1a** (1.37 g) was added at 0 °C, and the mixture was stirred at rt for 1 h. [A small sample of **2** was filtered under nitrogen and characterized by ^{1}H NMR: (300 MHz, CD_3CN) δ 13.06 (br s, 1H), 8.28 (d, J = 12.3 Hz, 1H), 8.18 (d, J = 8.9 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 3.56 (s, 3H), 3.73 (s, 3H).] To the resulting suspension of **2** was added a solution of **3a** (1.07 g, 10.0 mmol) in CH_2Cl_2 (10 mL), followed by the dropwise addition of DIPEA (5.16 g, 40.0 mmol) with cooling to keep the reaction temperature below 20 °C. After 1 h at rt, 10% aq K_2CO_3 (20 mL) was added, and the aq layer was separated and extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, and the resulting residue was triturated with EtOAc (10 mL) to afford a 76% yield (2.14 g) of **4** as an off-white solid: mp 138−140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.93 (s, 1H), 7.86 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 3.04 (s, 3H), 2.95 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.9, 155.0, 154.1, 136.9, 132.0, 128.8, 128.6, 127.5, 120.21, 120.19, 33.9, 20.4. Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.94. Found: C, 72.29; H, 6.91; N, 14.76.

Deprotection of 4 to 4-Amino-*N*-(4-tolyl)benzamide (6a). 4 (140 mg, 0.50 mmol) was mixed with ethanol (3 mL) and ethylenediamine (135 mg, 2.25 mmol), and the mixture was heated at reflux overnight. The cooled mixture was evaporated to dryness, and the residue was triturated with water (10 mL) to afford **6a** in 80% yield (90 mg) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 6.59 (d, J = 8.6 Hz, 2H), 5.73 (s, 2H), 2.26 (s, 3H). The ^{1}H NMR spectrum of this product was consistent with literature data.[8]

General One-Pot Procedure for the Preparation of 3- and 4-Aminobenzanilides: 6-Amino-*N*-(4-nitrophenyl)nicotinamide (6j). 6-Aminonicotinic acid (1.38 g, 10.0 mmol) was added at 0 °C to Vilsmeier reagent (20.0 mmol) in CH_2Cl_2 (20 mL) prepared as described above, then the mixture was stirred at rt for 1 h. CH_2Cl_2 (10 mL) was added, followed by pyridine (2.45 g, 31.0 mmol) at 0 °C, then the mixture was stirred for 30 min at rt. 4-Nitroaniline (1.38 g, 10.0 mmol) was added, and the reaction was stirred for a further 1.5 h. It was then concentrated to dryness, and the residue was heated at reflux in ethanol (25 mL) with ethylenediamine (2.70 g, 45.0 mmol) for 30 min. The resulting mixture was evaporated to dryness, stirred with water (50 mL), and filtered. The filter cake was triturated with methanol (6 mL) to afford **6j** as a yellow solid (2.14 g, 83%): mp 275−277 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.65 (d, J = 2.2 Hz, 1H), 8.24 (d, J = 9.3 Hz, 2H), 8.04 (d, J = 9.3 Hz, 2H), 7.96 (dd, J = 8.8, 2.4 Hz, 1H), 6.78 (s, 2H), 6.52 (d, J = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.8, 162.0, 149.5, 145.9, 142.0, 136.7, 124.7, 119.4, 117.3, 112.3, 106.9. Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.56; H, 3.81; N, 21.41.

General One-Pot Procedure for the Preparation of 2-Aminobenzanilides: 2-Amino-*N*-(4-tolyl)benzamide (10a). The chlorinating-protecting reagent was prepared from *N*,*N*-diisopropylformamide (2.67 g, 20.7 mmol) and oxalyl chloride (2.52 g, 19.8 mmol) in CH_2Cl_2 (20 mL) following the above procedure for the preparation of Vilsmeier reagent. 2-Aminobenzoic acid (1.37 g, 10.0 mmol) was added at 0 °C, and the mixture was stirred at rt for 1 h. A solution of 4-methylaniline (1.07 g, 10.0 mmol) in CH_2Cl_2 (10 mL), followed by pyridine (2.45 g, 31.0 mmol), was added at 0 °C and the mixture was stirred at 0 °C for 30 min. After warming to room temperature, the reaction was evaporated to dryness. A solution of *N*,*N*′-dimethylethylenediamine (3.94 g, 44.7 mmol) in ethanol (25 mL) was added, and the mixture was heated at reflux, allowing the solvent to distill until the internal temperature reached 110 °C. The reflux was continued at that temperature for 14 h, at which point the reaction was complete. Evaporation to dryness, followed by trituration with water (50 mL) afforded an 82% yield (1.85 g) of **10a** as a white powder: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.60 (d, J = 6.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.19 (td, J = 7.7, 1.2 Hz, 1H), 7.13 (d, J = 8.3 Hz, 2H), 6.74

(37) Zumstein, F.; Assmann, E.; Koenigsberger, R.; Holzbauer, R.; Zumstein, F. German Patent 2012094, 1972.

(d, $J = 7.9$ Hz, 1H), 6.58 (t, $J = 7.4$ Hz, 1H), 6.30 (s, 2H), 2.27 (s, 3H). The ^{1}H NMR spectrum of this product was consistent with literature data.[8]

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Supporting Information Available: Detailed experimental procedures for all compounds prepared, characterization data, ^{1}H and ^{13}C NMR spectra for novel compounds, and ^{1}H NMR spectra for literature compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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