EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201402179

Cleavage of 2-(Arylamino)-4,6-dimethoxypyrimidines To Yield Arylguanidines

Julian W. Shaw,[a] David H. Grayson,[a] and Isabel Rozas*[a]

Keywords: Synthetic methods / Cleavage reactions / Nitrogen heterocycles / Protecting groups / Guanidine

A novel method for the synthesis of aryl-substituted guanidines in good overall yields is presented; it consists of the acidic cleavage of 2-(arylamino)-4,6-dimethoxypyrimidines, which were prepared by coupling aryl bromides with 2-amino-4,6-dimethoxypyrimidine. This methodology introduces a new means of protection for the guanidine functionality.

Introduction

Aryl-substituted guanidines have found a myriad of uses in medicinal chemistry, such as anesthetics,[1] antacid agents,[2] minor groove binders,[3–7] α_2-adrenoceptor antagonists,[8–10] and F_1F_0-ATPase inhibitors.[11] Their presence is ubiquitous in both marine and terrestrial natural products.[12] For those reasons, the synthesis of aryl-substituted guanidines has been extensively studied in recent years.[13,14] Existing methods for their assembly are often problematic because toxic reagents are used,[15] the guanidine precursor is expensive,[16] and there is a need for high molecular weight protecting groups.[8] All are potentially disadvantageous features of many syntheses. There is, therefore, a need for the development of more efficient protocols for their preparation. The aim of the present work was to devise an environmentally friendly, cost-effective, and atom-economical [compared to the use of typical carbamate protecting groups, e.g., *tert*-butoxycarbonyl (Boc) or benzyloxycarbonyl (CBz)] method to meet this need.

Results and Discussion

We first investigated the use of 2-(arylamino)pyrimidine derivatives as potential synthons for aryl-substituted guanidines. Inspired by the work of Al-Mourabit,[17] we planned to synthesize a number of 2-(arylamino)pyrimidines and examine the susceptibility of the pyrimidine ring system towards cleavage to unmask the corresponding *N*-aryl-substituted guanidines (Figure 1).

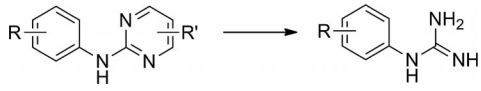


Figure 1. Potential for pyrimidine systems to yield guanidines.

We initially synthesized a family of 2-(arylamino)pyrimidines,[18] and with the realization that both Chichibabin[19] and Dimroth types of reaction[20] may be able to break the aromaticity of the pyrimidine moiety, we designed experiments to cleave the heteroaromatic ring. The simple 2-(phenylamino)pyrimidine (**1**) system was exposed separately to a number of sulfur, oxygen, and nitrogen nucleophiles and to a range of acidic and basic conditions at a wide variety of temperatures, but very low reactivity towards ring cleavage was generally observed (for selected examples, see entries 1, 2, and 4 in Table 1).

Table 1. Investigation into pyrimidine ring cleavage. All reactions were performed at 100 °C.

1, R = H
2, R = OMe

3

Entry	R	Reactant	Solvent	Yield [%][a]
1	H	$NH_2OH{\cdot}HCl$	EtOH	<5
2	H	1 M NaOH	H_2O	<5
3	OMe	1 M NaOH	H_2O	0[b]
4	H	4 M HCl	H_2O	<5
5	OMe	4 M HCl	H_2O	76
6	OMe	6 M HCl	H_2O	84
7	OMe	6 M HCl	H_2O/AcOH	100

[a] Based on recovered starting material. [b] No reaction occurred.

After extensive experimentation, we found that increasing the electron density of the pyrimidine system by introducing methoxy groups at both the 4- and 6-positions made it more susceptible to ring cleavage through hydrolytic pro-

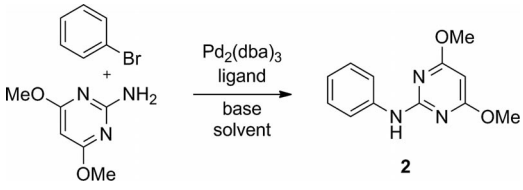
[a] School of Chemistry, Trinity Biomedical Sciences Institute, Trinity College Dublin,
152-160 Pearse St., Dublin 2, Ireland
E-mail: rozasi@tcd.ie
http://www.tcd.ie/Chemistry/staff/people/Rozas/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402179.

cesses. Thus, 4,6-dimethoxy-2-(phenylamino)pyrimidine (**2**) was chosen as a substrate with significant potential for more facile pyrimidine ring cleavage. A single literature example shows the instability of dimethoxypyrimidines to acidic conditions. Thus, Moulard and co-workers reported the preparation of 1-(3-ethylsulfonylpyridin-2-yl)guanidine as a side product by treating 2-[(3-ethylsulfonylpyridin-2-yl)-amino]-4,6-dimethoxypyrimidine with concentrated HCl.[21]

Initial investigations were very promising (Table 1, entry 5), and a screening of acidic reaction conditions showed that treatment of **2** with 6 M HCl at 100 °C in a 1:1 mixture of H_2O/AcOH led to complete cleavage of the pyrimidine ring to yield corresponding aryl-substituted guanidine hydrochloride **3** (Table 1, entry 7). Owing to the low solubility of the pyrimidine substrates, the use of AcOH as a co-solvent was necessary. On the basis of this encouraging result, we then optimized the synthesis of *N*-phenyl-2-amino-4,6-dimethoxypyrimidine (**2**) by utilizing Buchwald–Hartwig amination chemistry (Table 2).[22]

Table 2. Optimization of the Pd-mediated coupling of bromobenzene and 2-amino-4,6-dimethoxypyrimidine.[a]



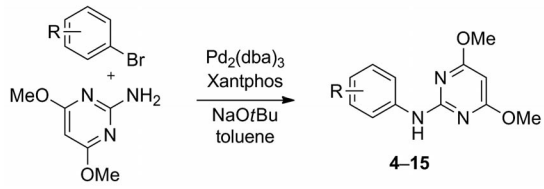
Entry	Ligand[b]	Base	Solvent	Yield [%]
1	Xphos	NaO*t*Bu	toluene	58
2	Xphos	NaO*t*Bu	1,4-dioxane	57
3	Xphos	K_3PO_4	toluene	50
4	BINAP	NaO*t*Bu	toluene	67
5	Xantphos	NaO*t*Bu	toluene	96

[a] Reaction conditions: $Pd_2(dba)_3$ (2-mol-%), ligand (3-mol-%), NaO*t*Bu (1.5 mmol), toluene (1.5 mL per mmol of aryl halide), 95 °C, 8–12 h; dba = dibenzylideneacetone. [b] Xphos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

The use of the most effective combination, that is, $Pd_2(dba)_3$, Xantphos, and NaO*t*Bu in toluene at 95 °C, generated the set of pyrimidines **4**–**15** in good to excellent yields (Table 3), and the reaction was reproducible on a multigram scale.[23] These conditions were tolerant of electron-withdrawing, electron-donating, and/or sterically bulky substituents located in different positions on the aryl ring (Table 3). In the particular cases of **10**–**14**, K_3PO_4 was used as a base owing to the presence of electron-withdrawing substituents on the aryl bromide ring. K_3PO_4 proved to be a superior base to NaO*t*Bu in these cases, as previously documented for Buchwald–Hartwig coupling reactions.[22b]

The members of the synthesized 2-(arylamino)-4,6-dimethoxypyrimidine family (i.e., **2**, **4**–**15**) were then exposed to the conditions that we had developed for pyrimidine ring cleavage, and each yielded (Table 4) the corresponding aryl-substituted guanidine (i.e., **3**, **16**–**27**) in good to excellent yields. Gratifyingly, the compounds could be obtained in high purity (as determined by ^{1}H NMR spectroscopy), and chromatography was not required.

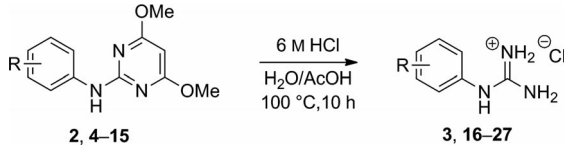
Table 3. Synthesis of substituted 2-(arylamino)-4,6-dimethoxypyrimidines **4**–**15**.[a]



Entry	R	Compound	Yield [%]
1	4-OMe	**4**	86
2	3-OMe	**5**	91
3	2-OMe	**6**	97
4	4-F	**7**	88
5	3-Br	**8**	94
6	2-F	**9**	84
7	4-CN	**10**	73[b]
8	3-CN	**11**	66[b]
9	2-CN	**12**	68[b]
10	4-NO_2	**13**	50[b]
11	3-NO_2	**14**	51[b]
12	2-Ph	**15**	68

[a] Reaction conditions: $Pd_2(dba)_3$ (2-mol-%), Xantphos (3-mol-%), NaO*t*Bu (1.5 mmol), toluene (1.5 mL per mmol of aryl halide), 95 °C, 8–12 h. [b] K_3PO_4 was used as the base.

Table 4. Examples of ring cleavage reactions.



Entry	R	Compound	Yield [%]
1	4-H	**3**	98
2	4-OMe	**16**	94
3	3-OMe	**17**	84
4	2-OMe	**18**	90
5	4-F	**19**	74
6	3-Br	**20**	87
7	2-F	**21**	84
8	4-CN/4-CO_2H[a]	**22**	62
9	3-CN/3-CO_2H[a]	**23**	75
10	2-CN	**24**	84
11	4-NO_2	**25**	46
12	3-NO_2	**26**	74
13	2-Ph	**27**	65

[a] Starting material R = CN; product R = CO_2H.

Not unexpectedly, a cyano group in the *meta* or *para* position of the aryl ring was partially converted into the corresponding carboxylic acid (see **22** and **23**) under these reaction conditions. Interestingly however, a cyano group in the *ortho* position remained intact throughout these hydrolysis reactions to yield **24**; we observed similar effects previously.[18]

It might be thought that the *ortho*-cyano group of aryl pyrimidine **12** is not hydrolyzed because of steric effects; however, the nitrile function is not bulky, and the pyrimid-

ine ring can rotate to avoid steric clash. Comparing the pK_a values (calculated with Marvin[24]) of the starting pyrimidines, we found that *ortho* derivative **12** had a pK_a = 10.7, whereas for *para* and *meta* isomers **10** and **11**, the pK_a was 12.4. We performed a computational study at the B3LYP/6-31+G** level[25] and optimized both starting 2-(cyanophenyl)pyrimidine (**12**) and corresponding final guanidinium salt **24**. In the case of **12**, there seems to be an attraction between the linking NH and the nitrile π system, whereas in final salt **24** this effect is even larger, which is indicative of an attractive interaction between the positive charge of the guanidinium moiety and the CN group. These calculations indicated that there were attractive interactions over the cyano group that protected it from hydrolysis.

Conclusions

We developed a novel method for the synthesis of aryl-substituted guanidines, which offers an inexpensive and environmentally friendly alternative to classical literature procedures.[1–17]

Experimental Section

General Procedure for the Coupling of Aryl Halides with 2-Amino-4,6-dimethoxypyrimidine: An oven-dried Schlenk tube was charged with a stir bar, $Pd_2(dba)_3$ (2 mol-%, 18 mg), and Xantphos (3 mol-%, 17 mg). 2-Amino-4,6-dimethoxypyrimidine (1.5 mmol, 1.5 equiv., 232 mg) was added, followed by base (1.5 mmol, 1.5 equiv.) and the aryl halide (1 mmol, 1 equiv.), if the aryl halide was a solid. The Schlenk tube was put under vacuum and back filled with argon three times. Freshly distilled toluene (1.5 mL mmol^{-1} aryl halide) was added. If the aryl halide was a liquid, it was now added to the solution. The Schlenk tube was then placed in an oil bath with vigorous stirring at 95 °C. The reaction was monitored by TLC, and once complete (typically 6–12 h), it was cooled to room temperature and diluted with EtOAc (10 mL). The reaction mixture was filtered through Celite, and any remaining residues in the Schlenk tube were washed out with EtOAc (10 mL). The organic phase was then washed with water (50 mL). The aqueous phase was extracted with EtOAc (3× 50 mL), and the combined organic layer was washed with brine (50 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude product was then purified by flash column chromatography (silica gel, 100% hexanes → 60% hexanes/40% ethyl acetate) to yield the target compound.

4,6-Dimethoxy-2-(phenylamino)pyrimidine (2):[26] Yield 96%. White solid. R_f = 0.5 (hexane/EtOAc, 80:20). M.p. 76–78 °C (ref.[26] 73–75 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 6 H), 5.58 (s, 1 H), 7.01 (t, J = 7.2 Hz, 1 H), 7.09 (br. s, NH), 7.31 (app t, 2 H), 7.62 (d, J = 8 Hz, 2 H) ppm. In agreement with literature values.[26]

4,6-Dimethoxy-2-[(4-methoxyphenyl)amino]pyrimidine (4): Yield 86% (224 mg). Off white crystal. R_f = 0.46 (hexane/EtOAc, 80:20). M.p. 86–87 °C. IR (film): $\tilde{\nu}$ = 3234, 3067, 2960, 1865, 1606, 1583, 1510, 1446, 1300, 1257, 1232, 1034, 1008, 885, 822, 787, 676, 660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 3.89 (s, 6 H), 5.54 (s, 1 H), 6.85 (br. s, NH), 6.87 (d, J = 9.2 Hz, 2 H), 7.51 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.8 (2 CH_3), 55.5 (CH_3), 80.6 (CH), 114.0 (2 CH), 121.0 (2 CH), 132.9 (qC), 155.3 (qC), 159.1 (qC), 171.9 (2 qC) ppm. HRMS: calcd. for $C_{13}H_{16}N_3O_3$ [M$^+$ + H] 262.1192; found 262.1194.

4,6-Dimethoxy-2-[(3-methoxyphenyl)amino]pyrimidine (5): Yield 91% (237 mg). Yellow oil. R_f = 0.49 (hexane/EtOAc, 80:20). IR (film): $\tilde{\nu}$ = 3397, 2947, 2834, 2216, 1604, 1571, 1446, 1413, 1355, 1285, 1191, 1156, 1059, 965, 911, 851, 799, 768, 729, 685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 3.92 (s, 6 H), 5.59 (s, 1 H), 6.59 (dd, J = 2.8, 8 Hz, 1 H), 7.05 (dd, J = 2.8, 8 Hz, 1 H), 7.11 (br. s, NH), 7.20 (app t, 1 H), 7.49 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.9 (2 CH_3), 55.1 (CH_3), 81.3 (CH), 104.7 (CH), 107.8 (CH), 111.2 (CH), 129.4 (CH), 141.1 (qC), 158.7 (qC), 160.1 (qC), 171.8 (2 qC) ppm. HRMS: calcd. for $C_{13}H_{16}N_3O_3$ [M$^+$ + H] 262.1192; found 262.1195.

4,6-Dimethoxy-2-[(2-methoxyphenyl)amino]pyrimidine (6): Yield 97% (252 mg). Off white solid. R_f = 0.57 (hexane/EtOAc, 80:20). M.p. 104–106 °C. IR (film): $\tilde{\nu}$ = 3430, 2938, 1576, 1481, 1437, 1416, 1382, 1294, 1247, 1192, 1160, 1028, 916, 768, 734, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 3.94 (s, 6 H), 5.57 (s, 1 H), 6.88–6.99 (m, 3 H), 7.59 (br. s, NH), 8.51–8.53 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.0 (2 CH_3), 55.5 (CH_3), 81.3 (CH), 109.8 (CH), 118.4 (CH), 120.8 (CH), 121.4 (CH), 129.4 (qC), 147.6 (qC), 158.8 (qC), 171.9 (2 qC) ppm. HRMS: calcd. for $C_{13}H_{16}N_3O_3$ [M$^+$ + H] 262.1192; found 262.1194.

2-[(4-Fluorophenyl)amino]-4,6-dimethoxypyrimidine (7): Yield 88% (220 mg). White solid. R_f = 0.42 (hexane/EtOAc, 80:20). M.p. 92–94 °C. IR (film): $\tilde{\nu}$ = 3428, 2969, 1614, 1578, 1544, 1507, 1463, 1373, 1357, 1274, 1192, 1104, 1011, 858, 824, 781, 747, 713 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 6 H), 5.57 (s, 1 H), 6.96 (br. s, NH), 6.98–7.03 (m, 2 H), 7.53–7.57 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.9 (2 CH_3), 81.0 (CH), 115.2 (d, $J_{C,F}$ = 23 Hz, 2 CH), 120.7 (d, $J_{C,F}$ = 15 Hz, 2 CH), 136.6 (qC), 158.8 (q, C1), 159.4 (d, $J_{C,F}$ = 240 Hz, CF), 172.0 (2 qC) ppm. HRMS: calcd. for $C_{12}H_{12}FN_3O_2$ [M$^+$ + H] 250.0992; found 250.0994.

2-[(3-Bromophenyl)amino]-4,6-dimethoxypyrimidine (8): Yield 94% (292 mg). Off white solid. R_f = 0.39 (hexane/EtOAc, 80:20). M.p. 84–86 °C. IR (film): $\tilde{\nu}$ = 3423, 2945, 1604, 1578, 1481, 1420, 1360, 1301, 1230, 1214, 1195, 1160, 1060, 1008, 933, 872, 766, 734, 676 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 6 H), 5.61 (s, 1 H), 6.93 (br. s, NH), 7.15 (m, 2 H), 7.36 (d, J = 7.2 Hz, 1 H), 8.12 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.0 (2 CH_3), 81.9 (CH), 117.2 (CH), 121.9 (CH), 122.5 (qC), 124.8 (CH), 129.9 (CH), 141.0 (qC), 158.4 (qC), 171.4 (2 qC) ppm. HRMS: calcd. for $C_{12}H_{12}BrN_3O_2$ [M$^+$ + H] 310.0191; found 310.0190.

2-[(2-Fluorophenyl)amino]-4,6-dimethoxypyrimidine (9): Yield 84% (210 mg). Yellow oil. R_f = 0.54 (hexane/EtOAc, 80:20). IR (film): $\tilde{\nu}$ = 3431, 3312, 2945, 1622, 1572, 1536, 1433, 1415, 1357, 1212, 1192, 1159, 1103, 1059, 981, 878, 849, 740, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 6 H), 5.61 (s, 1 H), 6.94 (m, 1 H), 7.06–7.14 (m, 2 H), 7.16 (br. s, NH), 8.50 (app t, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.0 (2 CH_3), 81.7 (CH), 114.6 (d, $J_{C,F}$ = 20 Hz, CH), 120.4 (CH), 121.9 (d, $J_{C,F}$ = 8 Hz, CH), 124.1 (d, $J_{C,F}$ = 3 Hz, CH), 128.1 (d, $J_{C,F}$ = 9 Hz, qC), 153.5 (d, $J_{C,F}$ = 260 Hz, CF), 158.4 (qC), 171.9 (2 qC) ppm. HRMS: calcd. for $C_{12}H_{12}FN_3O_3$ [M$^+$ + H] 250.0992; found 250.0994.

2-[(4-Cyanophenyl)amino]-4,6-dimethoxypyrimidine (10): Yield 73% (167 mg). White powder. R_f = 0.31 (hexane/EtOAc, 80:20). M.p. 144–145 °C. IR (film): $\tilde{\nu}$ = 3423, 3397, 2947, 2220, 1601, 1576, 1510, 1480, 1455, 1359, 1305, 1281, 1193, 1161, 1060, 1008, 933, 872, 766, 707, 687 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 6 H), 5.66 (s, 1 H), 7.16 (br. s, NH), 7.59 (d, J = 8 Hz, 2 H), 7.75 (d, J = 8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.3 (2

CH_3), 82.5 (CH), 104.6 (qC), 118.3 (2 CH), 119.4 (qC), 133.2 (2 CH), 143.7 (qC), 157.8 (qC), 171.9 (2 qC) ppm. HRMS: calcd. for $C_{13}H_{13}N_4O_2$ [M^+ + H] 257.1039; found 257.1038.

2-[(3-Cyanophenyl)amino]-4,6-dimethoxypyrimidine (11): Yield 66% (168 mg). Yellow/white solid. R_f = 0.30 (hexane/EtOAc, 80:20). M.p. 141–143 °C. IR (film): $\tilde{\nu}$ = 3327, 2950, 2230, 1607, 1572, 1543, 1463, 1432, 1363, 1286, 1244, 1194, 1163, 1113, 1060, 1005, 984, 847, 804, 787, 769, 699, 684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 6 H), 5.64 (s, 1 H), 7.20 (br. s, NH), 7.26 (d, J = 7.6 Hz, 1 H), 7.37 (app t, 1 H), 7.65 (d, J = 8 Hz, 1 H), 8.22 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.1 (2 CH_3), 81.9 (CH), 112.7 (qC), 119.2 (qC), 121.9 (CH), 122.9 (CH), 125.4 (CH), 129.6 (CH), 140.4 (qC), 158.2 (qC), 171.9 (2 qC) ppm. HRMS: calcd. for $C_{13}H_{13}N_4O_2$ [M^+ + H] 257.1039; found 257.1039.

2-[(2-Cyanophenyl)amino]-4,6-dimethoxypyrimidine (12): Yield 70% (179 mg). White powder. R_f = 0.39 (hexane/EtOAc, 80:20). M.p. 132–134 °C. IR (film): $\tilde{\nu}$ = 3399, 3123, 3012, 2948, 2861, 2215, 1638, 1604, 1570, 1540, 1496, 1471, 1415, 1358, 1282, 1108, 1006, 948, 871, 803, 769, 689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 6 H), 5.67 (s, 1 H), 7.04 (t, J = 8 Hz, 1 H), 7.43 (br. s, NH), 7.53–7.58 (m, 2 H), 8.61 (d, J = 9.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.2 (2 CH_3), 82.8 (CH), 100.9 (qC), 117.0 (qC), 119.6 (CH), 121.8 (CH), 132.5 (CH), 133.7 (CH), 142.5 (qC), 157.7 (qC), 171.8 (2 qC) ppm. HRMS: calcd. for $C_{13}H_{13}N_4O_2$ 257.1039 [M^+ + H]; found 257.1033.

4,6-Dimethoxy-2-[(4-nitrophenyl)amino]pyrimidine (13): Yield 50%. Yellow powder. R_f = 0.55 (hexane/EtOAc, 1:1). M.p. 198–201 °C. IR (film): $\tilde{\nu}$ = 3374, 2961, 2918, 2849, 2491, 1596, 1573, 1546, 1488, 1389, 1318, 1303, 1260, 1191, 1110, 1055, 929, 846, 795, 686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.97 (s, 6 H), 5.71 (s, 1 H), 7.74 (br. s, NH), 7.79 (d, J = 8.8 Hz, 2 H), 8.22 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.3 (2 CH_3), 80.2 (CH), 115.4 (2 CH), 122.7 (2 CH), 139.5 (qC), 142.6 (qC), 154.4 (qC), 169.0 (2 qC) ppm. HRMS: calcd. for $C_{12}H_{13}N_4O_4$ [M^+ + H] 277.0937; found 277.0942.

4,6-Dimethoxy-2-[(3-nitrophenyl)amino]pyrimidine (14): Yield 51%. Yellow powder. R_f = 0.56 (hexane/EtOAc, 1:1). M.p. 171–172 °C. IR (film): $\tilde{\nu}$ = 3374, 2961, 2918, 2849, 2491, 1596, 1576, 1546, 1488, 1389, 1318, 1303, 1260, 1191, 1110, 1055, 929, 846, 795, 686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.99 (s, 6 H), 5.67 (s, 1 H), 7.44 (app t, 1 H), 7.60 (dd, J = 1.2, 8 Hz, 1 H), 7.72 (br. s, NH), 7.86 (dd, J = 1.2, 8 Hz, 1 H), 9.12 (app t, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.5 (2 CH_3), 81.6 (CH), 113.5 (CH), 117.0 (CH), 124.2 (CH), 129.4 (CH), 140.6 (qC), 148.9 (qC), 157.8 (qC), 171.8 (2 qC) ppm. HRMS: calcd. for $C_{12}H_{13}N_4O_4$ [M^+ + H] 277.0937; found 277.0940.

2-[(1,1′-Biphenyl-2-yl)amino]-4,6-dimethoxypyrimidine (15): Yield 68% (208 mg). Fluffy white solid. R_f = 0.58 (hexane/EtOAc, 80:20). M.p. 81–82 °C. IR (film): $\tilde{\nu}$ = 3423, 2942, 1602, 1578, 1537, 1481, 1359, 1283, 1195, 1060, 943, 857, 774, 759, 737, 688 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 6 H), 5.56 (s, 1 H), 6.92 (br. s, NH), 7.09 (app t, 1 H), 7.23 (m, 1 H), 7.34–7.50 (m, 6 H), 8.49 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.0 (2 CH_3), 80.9 (CH), 120.4 (CH), 122.3 (CH), 127.7 (CH), 128.0 (CH), 129.0 (2 CH), 129.5 (2 CH), 130.2 (CH), 131.7 (qC), 136.5 (qC), 138.6 (qC), 158.8 (qC), 171.9 (qC) ppm. HRMS: calcd. for $C_{18}H_{18}N_3O_3$ [M^+ + H] 308.1399; found 308.1393.

General Procedure for the Cleavage of 2-(Arylamino)-4,6-dimethoxypyrimidine: Water (0.21 mL) and 12 M HCl (0.42 mL, 20 equiv.) were added to a mixture of 2-(arylamino)-4,6-dimethoxypyrimidine (0.25 mmol, 1 equiv.) in AcOH (0.21 mL), and the mixture was heated to reflux. For the reaction to proceed successfully, the round-bottomed flask needed to be covered with aluminum foil and fully submerged in an oil bath at 100 °C. The reaction was monitored by TLC; all TLC samples were basified by using Et_3N. Once the reaction was deemed complete, it was allowed to cool to room temperature. The solution was washed with EtOAc (3 × 10 mL) and CH_2Cl_2/MeOH (20% MeOH, 1 × 10 mL) to remove any unreacted starting materials, and then the aqueous phase was concentrated under reduced pressure to yield the target aryl-substituted guanidine as the hydrochloride salt.

Phenylguanidine Hydrochloride (3): Yield 10–98%. ^1H NMR (400 MHz, D_2O): δ = 7.06 (d, J = 7.6 Hz, 2 H), 7.23 (d, J = 7 Hz, 1 H), 7.31 (t, J = 7.2 Hz, 2 H) ppm. HRMS: calcd. for $C_7H_{10}N_3$ [M^+ + H] 136.0875; found 136.0870. In agreement with literature values.[10]

1-(4-Methoxyphenyl)guanidine Hydrochloride (16): Yield 94%. IR (film): $\tilde{\nu}$ = 3398, 3131, 2978, 2497, 1671, 1630, 1293, 1176, 1015, 828, 682 cm^{-1}. ^1H NMR (400 MHz, D_2O): δ = 3.71 (s, 3 H), 6.92 (d, J = 7.2 Hz, 2 H), 7.14 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 58.0 (CH_3), 117.8 (2 CH), 129.4 (qC), 130.6 (2 CH), 159.2 (qC), 161.2 (qC) ppm. HRMS: calcd. for $C_8H_{12}N_3O$ [M^+ + H] 166.0980; found 166.0973.

1-(3-Methoxyphenyl)guanidine Hydrochloride (17): Yield 84%. IR (film): $\tilde{\nu}$ = 3147, 2430, 1660, 1579, 1457, 1205, 1040, 857, 690 cm^{-1}. ^1H NMR (400 MHz, D_2O): δ = 3.70 (s, 3 H), 6.79 (m, 2 H), 6.87 (d, J = 8 Hz, 1 H), 7.29 (app t, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 55.6 (CH_3), 113.4 (CH), 113.5 (CH), 118.2 (CH), 136.3 (qC), 159.4 (qC), 160.1 (qC) ppm. HRMS: calcd. for $C_8H_{12}N_3O$ [M^+ + H] 166.0980; found 166.0983.

1-(2-Methoxyphenyl)guanidine Hydrochloride (18): Yield 90%. IR (film): $\tilde{\nu}$ = 3312, 3155, 2972, 2462, 1667, 1455, 1287, 1161, 1045, 789 cm^{-1}. ^1H NMR (400 MHz, D_2O): δ = 3.75 (s, 3 H), 6.95 (app t, 1 H), 7.05 (d, J = 8 Hz, 1 H), 7.17 (d, J = 8 Hz, 1 H), 7.31 (app t, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 55.8 (CH_3), 113.0 (CH), 121.4 (CH), 122.0 (qC), 128.2 (CH), 130.1 (CH), 154.4 (qC), 156.6 (qC) ppm. HRMS: calcd. for $C_8H_{12}N_3O$ [M^+ + H] 166.0980; found 166.0977.

1-(4-Fluorophenyl)guanidine Hydrochloride (19): Yield 74%. IR (film): $\tilde{\nu}$ = 3311, 3139, 1665, 1590, 1507, 1215, 831, 793 cm^{-1}. ^1H NMR (400 MHz, D_2O): δ = 7.20–7.24 (m, 2 H), 7.28–7.41 (m, 2 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 119.2 (d, $J_{C,F}$ = 9 Hz, 2 C), 131.1 (d, $J_{C,F}$ = 9 Hz, 2 C), 132.5 (d, qC, $J_{C,F}$ = 2.3 Hz), 159.1 (qC), 163.1 (d, qC, $J_{C,F}$ = 244 Hz) ppm. HRMS: calcd. for $C_7H_8FN_3$ [M^+ + H] 154.0781; found 154.0771.

1-(3-Bromophenyl)guanidine Hydrochloride (20): Yield 87%. IR (film): $\tilde{\nu}$ = 3319, 3133, 1668, 1568, 1476, 1301, 1069, 859, 671 cm^{-1}. ^1H NMR (600 MHz, D_2O): δ = 7.17 (d, J = 8 Hz, 1 H), 7.27 (app t, 1 H), 7.42 (s, 1 H), 7.45 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 122.2 (qC), 124.5 (CH), 128.6 (CH), 130.8 (CH), 131.2 (CH), 135.4 (qC), 156.1 (qC) ppm. HRMS: calcd. for $C_7H_9BrN_3$ [M^+ + H] 213.9980; found 213.9984.

1-(2-Fluorophenyl)guanidine Hydrochloride (21): Yield 84%. IR (film): $\tilde{\nu}$ = 3323, 3146, 1672, 1621, 1501, 1423, 1264, 1106, 759 cm^{-1}. ^1H NMR (600 MHz, D_2O): δ = 7.17–7.27 (m, 4 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 116.6 (d, $J_{C,F}$ = 16 Hz), 121.4 (d, $J_{C,F}$ = 16 Hz, qC), 125.2 (CH), 128.7 (CH), 130.4 (d, J = 6 Hz, qC), 153.3 (qC), 156.5 (d, $J_{C,F}$ = 206 Hz, CF) ppm. HRMS: calcd. for $C_7H_8FN_3$ [M^+ + H] 154.0781; found 154.0775.

1-(4-Carboxyphenyl)guanidine Hydrochloride (22): 62%. IR (film): $\tilde{\nu}$ = 3314, 2456, 2345, 2329, 2311, 1693, 1622, 1567, 1345, 1117,

1040, 827, 764 cm^{-1}. ^{1}H NMR (400 MHz, D_2O): δ = 7.39 (d, J = 8 Hz, 2 H), 8.03 (d, J = 8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 124.2 (2 CH), 129.0 (qC), 131.2 (2 CH), 139.0 (qC), 155.9 (qC), 170.1 (qC) ppm. HRMS: calcd. for $C_8H_{10}N_3O_2$ [M^+ + H] 180.0773; found 180.0764.

1-(3-Carboxyphenyl)guanidine Hydrochloride (23): Yield 75%. IR (film): $\tilde{\nu}$ = 3369, 3171, 3069, 2871, 2345, 1699, 1654, 1577, 1346, 1215, 1082, 767 cm^{-1}. ^{1}H NMR (400 MHz, D_2O): δ = 7.57 (d, J = 8 Hz, 1 H), 7.61 (app t, 1 H), 7.90 (s, 1 H), 7.99 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 126.6 (CH), 128.7 (CH), 130.2 (CH), 130.4 (CH), 132.1 (qC), 134.5 (qC), 156.3 (qC), 169.9 (qC) ppm. HRMS: calcd. for $C_8H_{10}N_3O_2$ [M^+ + H] 180.0773; found 180.0766.

1-(2-Cyanophenyl)guanidine Hydrochloride (24): Yield 84%. IR (film): $\tilde{\nu}$ = 3302, 3103, 3044, 2879, 2260, 1685, 1479, 1415, 1157, 751 cm^{-1}. ^{1}H NMR (400 MHz, D_2O): δ = 7.31 (d, J = 8 Hz, 1 H), 7.45 (app t, 1 H), 7.81 (app t, 1 H), 7.98 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 114.4 (qC), 116.7 (CH), 125.9 (CH), 126.9 (CH), 137.0 (CH), 137.6 (qC), 150.2 (qC), 161.4 (qC) ppm. HRMS: calcd. for $C_8H_9N_4$ [M^+ + H] 161.0827; found 161.0828.

1-(4-Nitrophenyl)guanidine Hydrochloride (25): Yield 46%. IR (film): $\tilde{\nu}$ = 3186, 1707, 1672, 1582, 1420, 1341, 1247, 1170, 853, 697 cm^{-1}. ^{1}H NMR (400 MHz, D_2O): δ = 7.38 (d, J = 8.8 Hz, 2 H), 8.20 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 124.2 (2 CH), 125.4 (2 CH), 141.5 (qC), 145.3 (qC), 155.7 (qC) ppm. HRMS: calcd. for $C_7H_9N_4O_2$ [M^+ + H] 181.1640; found 181.1645.

1-(3-Nitrophenyl)guanidine Hydrochloride (26): Yield 74%. IR (film): $\tilde{\nu}$ = 3313, 3115, 2582, 1671, 1631, 1525, 1416, 1349, 1249, 1093, 832, 805, 660 cm^{-1}. ^{1}H NMR (400 MHz, D_2O): δ = 7.55–7.61 (m, 2 H), 8.08–8.10 (m, 2 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 119.9 (CH), 122.7 (CH), 131.1 (CH), 132.0 (CH), 136.0 (qC), 148.7 (qC), 169.1 (qC) ppm. HRMS: calcd. for $C_7H_9N_4O_2$ [M^+ + H] 181.1640; found 181.1642.

1-(1,1′-Biphenyl-2-yl)guanidine Hydrochloride (27): Yield 65%. IR (film): $\tilde{\nu}$ = 3146, 2407, 1709, 1611, 1480, 1228, 763 cm^{-1}. ^{1}H NMR (400 MHz, D_2O): δ = 7.43–7.58 (m, 9 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 127.8 (CH), 128.5 (CH), 128.6 (2 CH), 128.6 (2 CH), 129.1 (CH), 129.3 (CH), 131.1 (CH), 138.0 (qC), 139.8 (qC), 156.2 (qC), 171.3 (qC) ppm. HRMS: calcd. for $C_{13}H_{14}N_3$ [M^+ + H] 212.1188; found 212.1178.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectra and computational results.

Acknowledgments

This work was funded by the School of Chemistry, University of Dublin, Trinity College (grant to J. W. S.). The authors would like to thank Drs. John O'Brien, Manuel Ruether, Martin Feeney, and Gary Hessman for spectroscopic data.

[1] S. S. Patel, C. J. Dunn, H. M. Bryson, *CNS Drugs* **1996**, *6*, 474–497.
[2] T. J. Humphries, G. J. Merritt, *Aliment. Pharmacol. Ther.* **1999**, *13*, 18–26 (Suppl. 3).
[3] C. McKeever, M. Kaiser, I. Rozas, *J. Med. Chem.* **2013**, *56*, 700–711.
[4] P. S. Nagle, F. Rodriguez, S. J. Quinn, D. H. O'Donovan, J. M. Kelly, B. Nguyen, W. D. Wilson, I. Rozas, *Org. Biomol. Chem.* **2010**, *8*, 5558–5567.
[5] P. S. Nagle, F. Rodriguez, A. Kahvedzic, S. Quinn, I. Rozas, *J. Med. Chem.* **2009**, *52*, 7113–7121.
[6] F. Rodriguez, I. Rozas, M. Kaiser, R. Brun, B. Nguyen, W. D. Wilson, R. N. Garcia, C. J. Dardonville, *J. Med. Chem.* **2008**, *51*, 909–923.
[7] C. Bailly, R. K. Arafa, F. A. Tanious, W. Laine, C. Tardy, A. Lansiaux, P. Colson, D. W. Boykin, W. D. Wilson, *Biochemistry* **2005**, *44*, 1941–1952.
[8] F. Rodriguez, I. Rozas, A. M. Erdozain, J. J. Meana, L. F. Callado, *J. Med. Chem.* **2009**, *52*, 601–609.
[9] A. Goonan, A. Kahvedzic, F. Rodriguez, P. Nagle, T. McCabe, I. Rozas, A. M. Erdozain, J. J. Meana, L. F. Callado, *Bioorg. Med. Chem.* **2008**, *16*, 8210–8217.
[10] F. Rodriguez, I. Rozas, J. E. Ortega, J. J. Meana, L. F. Callado, *J. Med. Chem.* **2008**, *51*, 3304–3312.
[11] G. Rosse, *ACS Med. Chem. Lett.* **2012**, *3*, 952–952.
[12] R. G. Berlinck, A. E. Trindade-Silva, M. F. Santos, *Nat. Prod. Rep.* **2012**, *29*, 1382–1406.
[13] T. Suhs, B. Konig, *Mini-Rev. Org. Chem.* **2006**, *3*, 315–331.
[14] T. R. M. Rauws, B. U. W. Maes, *Chem. Soc. Rev.* **2012**, *41*, 2463–2497.
[15] K. S. Kim, L. Qian, *Tetrahedron Lett.* **1993**, *34*, 7677–7680.
[16] T. J. Baker, Y. Rew, M. Goodman, *Pure Appl. Chem.* **2000**, *72*, 347–354. Goodman's reagent [1,3-di-Boc-2-(trifluoromethylsulfonyl)guanidine] is commercially available from Sigma–Aldrich priced at €79.60 g^{-1}.
[17] C. Schroif-Gregoire, N. Travert, A. Zaparucha, A. Al-Mourabit, *Org. Lett.* **2006**, *8*, 2961–2964.
[18] J. W. Shaw, D. H. Grayson, I. Rozas, *ARKIVOC* **2014**, *2*, 161–174.
[19] For a review of Chichibabin reaction see: C. K. McGill, A. Rappa, *Adv. Heterocycl. Chem.* **1988**, *44*, 1–79.
[20] For a review of the Dimroth reaction, see: T. Fujii, T. Itaya, *Heterocycles* **1998**, *48*, 359–390.
[21] J. Rouchaud, O. Neus, C. Moulard, *Bull. Soc. Chim. Belg.* **1997**, *106*, 151–157.
[22] For reviews on C–N bond-forming cross-coupling reactions, see: a) J. Bariwalab, E. van der Eycken, *Chem. Soc. Rev.* **2013**, *42*, 9283–9303; b) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50.
[23] On a 2 g scale, a yield of 95% was obtained for the reaction of bromobenzene with 2-amino-4,6-dimethoxypyrimidine under the optimized conditions.
[24] *Marvin*, v. 6.0, ChemAxon, http://www.chemaxon.com/.
[25] These computations were performed by using the Gaussian09 package; see full reference in the Supporting Information.
[26] X. Chen, J. Wu, Z.-C. Shang, M.-F. Chen, Y.-P. Sun, J. Ly, M.-K. Lei, P.-Z. Zhang, *Tetrahedron Lett.* **2008**, *49*, 495–499.

Received: March 3, 2014
Published Online: April 23,2014

