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Report

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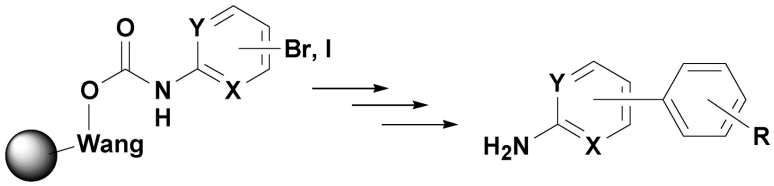

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Attachment of Unreactive Amines to the Solid Support: Synthesis of Phenyl-Substituted Anilines, 2-Aminopyridines, and 2-Aminopyrimidines

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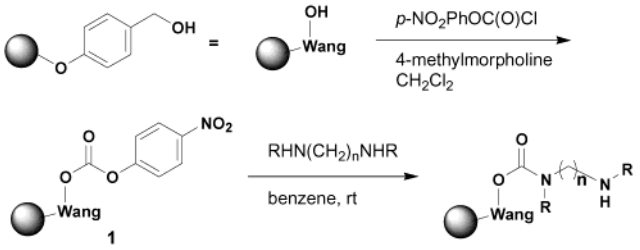
The biphenyl substructure and its heteroaromatic congeners are frequently occurring motifs in commercially available drugs.[1] For example, aryl 2-aminopyridines have been reported for the treatment of nitric oxide synthase-mediated disorders.[2] Similarly, aryl-substituted 2-aminopyridines and 2-aminopyrimidines are useful for the treatment of diseases modulated by the adenosine receptor.[3] As a result of these biological activities, we became interested in preparing solid-phase combinatorial libraries based on these structures, particularly those which contained aryl and heteroarylamines. Reported herein is a novel method for attaching anilines, 2-aminopyridines, and 2-aminopyrimidines to the solid support via a carbamate linker that facilitates the construction of libraries of phenyl-substituted anilines, 2-aminopyridines, and 2-aminopyrimidines.

The use of a carbamate linker can be traced back to Letsinger's attachment of amino acids via their N terminus to hydroxymethyl polystyrene for the synthesis of dipeptides.[4] A convenient way to form the carbamate linker utilizes the activated carbonate **1,** which was first reported by Leznoff as a monoblocking agent of symmetrical diamines (Scheme 1).[5] Carbonate **1** is a robust polymer-bound reagent for solid-phase synthesis that can be produced on a large scale and stored for at least 6 months without loss of activity.[6] Carbamate formation is straightforward with aliphatic amines, as evidenced by numerous reports in the literature,[7] but this method is problematic with anilines, aminopyridines and aminopyrimidines. In a preliminary experiment, the activated carbonate **1** (60 mg, 0.74 mmol/g) was treated with 2-amino-5-bromopyridine (5 equiv) and triethylamine (5 equiv) in 2 mL of anhydrous dichloromethane (DCM) at room temperature overnight. Following a standard washing protocol, the resin was treated with a 1:1 mixture of trifluoroacetic acid (TFA) and DCM to afford only 4-nitrophenol instead of the expected 2-amino-5-bromopyridine product. Presumably, the 2-amino-5-bromopyridine is not sufficiently nucleophilic to displace 4-nitrophenoxide from the carbonate resin. An alternative procedure[8] for carbamate formation with anthranilic acid using hydroxybenzotriazole (HOBt) and *N*,*N*-diisopropylethylamine (DIEA) in DCM/DMF (2:1) was also unsuccessful for our substrate, providing a 1:1 mixture of HOBt and 4-nitrophenol (as determined by ^{1}H NMR) upon cleavage. Kelly and McNeil's solution-phase method[9] for the Boc protection of arylamines provided evidence that deprotonating 2-amino-5-bromopyridine with sodium bis-(trimethylsilyl)amide (NaHMDS) would improve its reactivity with **1**.[10] Indeed, we found that the application of this method to carbamate formation on the solid support provided resin **2**, as shown in Scheme 2.[11] Upon treatment with a 1:1 mixture of TFA/DCM, resin **2** afforded a quantitative yield[12] of 2-amino-5-bromopyridine in high purity. As shown in Table 1 (entries 1−8), similar results were obtained for a range of bromo- and iodo-substituted anilines and 2-aminopyridines. However, this method was less successful for 2-amino-5-bromopyrimidine (37% purity) and 2-amino-5-iodopyrimidine (31% purity). LC/MS analysis indicated that the major side product was formed via nucleophilic substitution of the halogen atom on the pyrimidine ring by another halogenated 2-aminopyrimidine. This prompted us to examine whether the side reaction could be suppressed by reducing the amount of reagents and adding the NaHMDS to a preformed suspension of pyrimidine and resin. We were gratified to find that this modified procedure[13] dramatically improved the purity of the cleaved pyrimidine products (Table 1, entries 9 and 10).

As shown in Scheme 3, solid-supported iodo-substituted anilines, 2-aminopyridines, and 2-aminopyrimidines readily

Scheme 1



Scheme 2

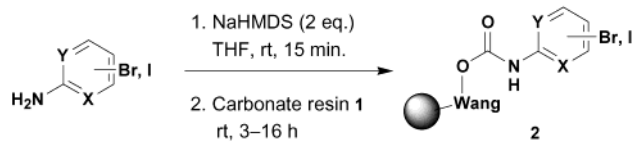


Table 1. Yield and Purity Data for Carbamate-Linked Aryl and Heteroarylamines

entry	amine	MH^+ (LC/MS)	purity (%)	yield (%)
1	2-amino-5-bromopyridine	173/175	100	94
2	2-amino-5-iodopyridine	221	97	100
3	2-bromoaniline	172/174	82	66
4	3-bromoaniline	172/174	100	77
5	4-bromoaniline	172/174	>95[14]	87
6	2-iodoaniline	220	100	99
7	3-iodoaniline	220	100	91
8	4-iodoaniline	220	85	63
9	2-amino-5-bromopyrimidine	174/176	97	66
10	2-amino-5-iodopyrimidine	222	100	71

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Scheme 3

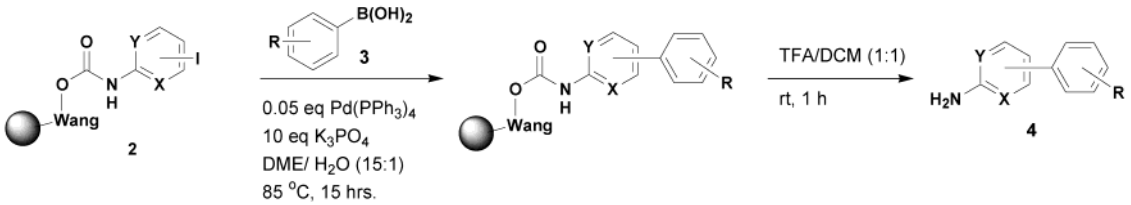

Table 2. Purity and Yield Data for 45 Phenyl-substituted Aryl and Heteroarylamines

			product characterization (**4**)		
entry	aryl iodides (**2**)	aryl boronic acids (**3**)	MH^+ (LC/MS)	purity (%)	yield (%)
1	2-iodoaniline	phenylboronic acid	170	82	87
2		3-aminobenzeneboronic acid	185	74	90
3		4-fluorophenylboronic acid	188	80	81
4		4-tolylboronic acid	184	94	70
5		4-methoxyphenylboronic acid	200	88	50
6		2-methylphenylboronic acid	184	68	58
7		4-(dimethylamino)phenylboronic acid	213	80	57
8		4-cyanophenylboronic acid	195	93	57
9		(4-methoxycarbonylphenyl)boronic acid	228	96	59
10	3-iodoaniline	phenylboronic acid	170	100	43
11		3-aminobenzeneboronic acid	185	100	46
12		4-fluorophenylboronic acid	188	100	40
13		4-tolylboronic acid	184	94	32
14		4-methoxyphenylboronic acid	200	95	22
15		2-methylphenylboronic acid	184	92	50
16		4-(dimethylamino)phenylboronic acid	213	98	31
17		4-cyanophenylboronic acid	195	98	51
18		(4-methoxycarbonylphenyl)boronic acid	228	98	52
19	4-iodoaniline	phenylboronic acid	170	81	31
20		3-aminobenzeneboronic acid	185	65	37
21		4-fluorophenylboronic acid	188	83	26
22		4-tolylboronic acid	184	91	37
23		4-methoxyphenylboronic acid	200	62	18
24		2-methylphenylboronic acid	184	72	23
25		4-(dimethylamino)phenylboronic acid	213	52	17
26		4-cyanophenylboronic acid	195	77	34
27		(4-methoxycarbonylphenyl)boronic acid	228	74	20
28	2-amino-5-iodopyridine	phenylboronic acid	171	94	60
29		3-aminobenzeneboronic acid	186	82	42
30		4-fluorophenylboronic acid	189	92	57
31		4-tolylboronic acid	185	90	53
32		4-methoxyphenylboronic acid	201	89	48
33		2-methylphenylboronic acid	185	92	50
34		4-(dimethylamino)phenylboronic acid	214	88	49
35		4-cyanophenylboronic acid	196	77	54
36		(4-methoxycarbonylphenyl)boronic acid	229	83	46
37	2-amino-5-iodopyrimidine	phenylboronic acid	172	96	35
38		3-aminobenzeneboronic acid	187	87	22
39		4-fluorophenylboronic Acid	190	93	25
40		4-tolylboronic Acid	186	94	39
41		4-methoxyphenylboronic acid	202	90	26
42		2-methylphenylboronic acid	186	94	32
43		4-(dimethylamino)phenylboronic acid	215	90	33
44		4-cyanophenylboronic acid	197	81	13
45		(4-methoxycarbonylphenyl)boronic acid	229	64	18

undergo Suzuki coupling reactions with phenyl boronic acids under standard conditions[15,16] to afford the corresponding phenyl-substituted products. To demonstrate the efficiency of the solid-phase route, a library of 45 phenyl-substituted aryl and heteroarylamines was synthesized by coupling five immobilized iodo-substituted aryl and heteroarylamines with nine substituted phenylboronic acids. This chemistry was carried out using IRORI MicroKans, and the yields and purities of the 45 products are listed in Table 2.

As reported in Table 2, product purities ranged from 52 to 98%, while product yields ranged from 13 to 90%. To better understand the origin of this variability, we calculated average purities and yields on a "per reagent" basis. These data are summarized in Table 3, where entries 1−5 correspond to the iodo-substituted amine reagents (**2**), and entries 6−14 correspond to the phenylboronic acid reagents (**3**). Low average yields were observed for two amine reagents, 4-iodoaniline (entry 3) and 2-amino-5-iodopyri-

Table 3. Average Purities and Yields Evaluated by Reagent

entry	reagent	N	% purity[a]	% yield[a]
1	2-iodoaniline	9	84 ± 3	68 ± 5
2	3-iodoaniline	9	97 ± 1	41 ± 4
3	4-iodoaniline	9	73 ± 4	27 ± 3
4	2-amino-5-iodopyridine	9	87 ± 2	51 ± 2
5	2-amino-5-iodopyrimidine	9	88 ± 3	27 ± 3
6	phenylboronic acid	5	91 ± 4	51 ± 10
7	3-aminobenzeneboronic acid	5	82 ± 6	47 ± 11
8	4-fluorophenylboronic acid	5	90 ± 4	46 ± 11
9	4-tolylboronic acid	5	93 ± 1	46 ± 7
10	4-methoxyphenylboronic acid	5	85 ± 6	33 ± 7
11	2-methylphenylboronic acid	5	84 ± 6	43 ± 7
12	4-(dimethylamino)phenylboronic acid	5	82 ± 8	37 ± 7
13	4-cyanophenylboronic acid	5	85 ± 4	42 ± 8
14	(4-methoxycarbonylphenyl)boronic acid	5	83 ± 6	39 ± 8

[a] Standard error = $\sigma/(N^{1/2})$, where σ = standard deviation and N = number of observations.

midine (entry 5). On the basis of the initial amine loadings listed in Table 1, only 4-iodoaniline provided samples in significantly lower purity and yield relative to the other four amines (Table 1, entry 8), suggesting that the 27% average yield for samples synthesized from 2-amino-5-iodopyrimidine arises from premature cleavage of the carbamate linkage during the reaction sequence rather than low initial loading (see Table 1, entry 2). Although we did observe some resin leakage from the IRORI MicroKans during the synthesis of the library, it is difficult to explain why 2-amino-5-iodopyrimidine-equipped resin would leak to a greater extent than the other four amine-equipped resins. Of the nine phenylboronic acids utilized in this library, 4-methoxyboronic acid (Table 3, entry 10) gave the lowest yield. It should be noted that even a 20% yield of final product was sufficient to meet our requirements for screening.

In conclusion, we have developed an efficient method to attach unreactive amines such as anilines and aminopyridines and amino-pyrimidines to Wang resin via the carbamate linker. To exemplify the utility of this approach, a small library of phenyl-substituted aryl- and heteroarylamines was synthesized via Suzuki coupling of the immobilized aryl iodides with a range of phenylboronic acids.

Acknowledgment. We thank Mr. Weixu Zhai for providing us with resin-bound carbonate for this study.

Supporting Information Available. Procedures for attachment of unreactive amines to the solid support and for Suzuki coupling, and ^{1}H NMR data (with an internal standard to provide quantitation) for all samples listed in Tables 1 and 2 are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887−2893.
(2) Esser, C. K.; Hagmann, W. K.; Hoffman, W. F.; Shah, S. K.; Wong, K. K.; Chabin, R. M.; Guthikonda, R. K.; Maccoss, M.; Caldwell, C. G.; Durette, P. L. Patent WO 9618616, 1996.
(3) Borroni, E. M.; Huber-Trottmann, G.; Kilpatrick, G. J.; Norcross, R. D. Patent WO 0162233, 2001.
(4) (a) Letsinger, R. L.; Kornet, M. J.; Mahadevan, V.; Jerina, D. M. *J. Am. Chem. Soc.* **1964**, *86*, 5163−5165. (b) Letsinger, R. L.; Kornet, M. J. *J. Am. Chem. Soc.* **1963**, *85*, 3045−3046.
(5) Dixit, D. M.; Leznoff, C. C. *J. Chem. Soc. Chem. Commun.* **1977**, 798−799.
(6) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937−940.
(7) For other representative examples, see (a) Li, W.-R.; Lin, Y.-S.; Yo, Y.-C. *Tetrahedron Lett.* **2000**, *41*, 6619−6622. (b) Morton, G. C.; Salvino, J. M.; Labaudinière, R. F.; Herpin, T. F. *Tetrahedron Lett.* **2000**, *41*, 3029−3033. (c) Rossè, G.; Ouertani, F.; Schröder, H. *J. Comb. Chem.* **1999**, *1*, 397−401. (d) Veerman, J. J. N.; Rutjes, F. P. J. T.; van Maarseveen, J. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 6079−6082. (e) Dressman, B. A.; Singh, U.; Kaldor, S. W. *Tetrahedron Lett.* **1998**, *39*, 3631−3634. (f) Kaljuste, K.; Undén, A. *Tetrahedron Lett.* **1996**, *37*, 3031−3034.
(8) (a) Gouilleux, L.; Fehrentz, J.-A.; Winternitz, F.; Martinez, J. *Tetrahedron Lett.* **1996**, *37*, 7031−7034. (b) Berry, J. M.; Howard, P. W.; Thurston, D. E. *Tetrahedron Lett.* **2000**, *41*, 6171−6174.
(9) Kelly, T. A.; McNeil, D. W. *Tetrahedron Lett.* **1994**, *35*, 9003−9006.
(10) The same concept has been used to displace imidazole from the carbonylimidazole resin. See: Josey, J. A.; Tarlton, C. A.; Payne, C. E. *Tetrahedron Lett.* **1998**, *39*, 5899−5902.
(11) The general procedure for the carbamate formation can be found in the Supporting Information of this Report.
(12) The yield was determined by NMR with 2,5-dimethylfuran (DMFu) as internal standard. Gerritz, S. W.; Sefler, A. M. *J. Comb. Chem.* **2000**, *2*, 39−41.
(13) The modified procedure can be found in the Supporting Information of this Report.
(14) The purity determined by LCMS/UV was 36%, but on the basis of the comparison of the product ^{1}H NMR spectrum with a known sample of 4-bromoaniline, this compound was >95% pure.
(15) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177−9180, and references therein.
(16) The conditions for the Suzuki coupling described in the Supporting Information gave the products with the highest yield and purity among the variations we attempted.

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