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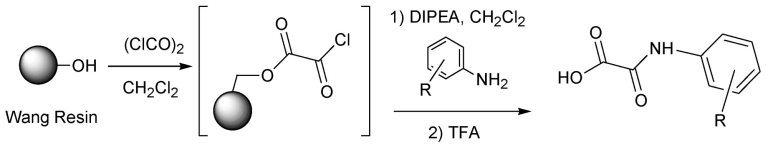

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Solid-Phase Synthesis of an Oxalic Acid Amide Library

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Monoamides of oxalic acid are of interest as bioisosteric replacements for phosphate groups in the design of new enzyme inhibitors. Here, we have demonstrated the use of oxalic acid as a linker to the Wang resin to synthesize individual or libraries of phosphate biosteres. The highly reactive resin-bound acid chloride reacts with arylamines to yield resin-bound *N*-aryloxamic acids (oxanilic acids). This methodology is especially useful for the rapid synthesis of 2-(oxalylamino)benzoic acids (OBAs), because it can be utilized for library synthesis and eliminates the intermediate purification step necessary in solution-phase reactions. The products are cleaved off the resin with trifluoroacetic acid in dichloromethane in good yields.

Introduction

When developing novel therapeutics based on phosphate mimics, an important criterion for inhibitor design has been the incorporation of stable, high-affinity, and minimally charged phosphate groups. Numerous phosphate group mimics have been reported, including squaryl groups,[1] acetic acids,[2,3] phosphonates,[4−7] malonates,[8−10] tetronic acids,[11] sulfonates,[12] sulfonyl and sulfonamido groups,[13] and oxamic acids.[14] Oxalyl groups have been reported in a variety of biologically active series. In particular, oxanilic acids have been recently reported as inhibitors of protein-tyrosine phosphatase 1B (PTP1B),[14,15] T-cell protein-tyrosine phosphatase,[16] and the tyrosine kinase $p56^{lck}$ SH2 domain.[17] Oxanilic acid esters have been found to be potent, orally active antiallergy agents.[18−21] It has also been reported[22] that substitution of the sarcosine residue of sarmesin with oxamic acid yields analogues with angiotensin antagonist activity.

Protein-tyrosine phosphatases (PTPs) are involved in the regulation of signal transduction processes as enzymes that catalyze the removal of phosphate groups from phosphotyrosine residues in peptides and proteins. They are interesting targets in several disease states, for example, cancer, inflammation, and diabetes. In particular, PTP1B is a cytosolic phosphatase, consisting of a single catalytic domain, the in vivo function of which involves the downstream regulation of insulin signaling by dephosphorylation of specific phosphotyrosine residues on the insulin receptor.[23] A common approach toward the rational development of PTP-specific inhibitors has been to incorporate nonhydrolyzable phosphotyrosine mimics into small PTP peptide substrates. An alternative approach has been the development of reversible, organic, small molecule inhibitors of PTPs.

Recently, a series of OBAs were reported to be general, reversible, competitive inhibitors for several PTPs, including CD45, PTP1B, PTPα, PTPβ, PTPϵ, PTP-LAR, and SHP1. The crystal structures of several 2-(oxalylamino)benzoic acids binding in the active site of PTB1B, have been reported.[15,24] 2-(Oxalylamino)benzoic acid binds to the active site of PTP1B with a K_i value of 20 μM against PTP1B at pH 5.5. At neutral pH, it binds with a weaker K_i of 200 μM for PTP1B and is considered one of the most potent minimal unit active site PTP1B inhibitors identified to date.[14] A number of conformational changes occur in the active site upon complexation with this ligand series. Specifically, Lys-120 undergoes a conformational change to form a unique salt bridge with the *o*-carboxylic acid of OBA. In addition the *o*-carboxylic acid of OBA appears to be within hydrogen bonding distance with Tyr47 and Asp181. The aromatic ring in the ligand forms favorable aromatic−aromatic interactions with a neighboring Phe182 in the protein. The optimal positioning of both of the carboxy groups of OBA is likely to contribute significantly to the potency of this class of compounds. Complexes of several OBA analogues with PTP1B have shown that the series can be modified to optimize the binding in the lipophilic binding site. The screening of libraries containing oxalyl groups attached to substituted aromatic ring systems could yield more potent PTP1B inhibitors.

The synthesis of OBA analogues has been recently reported by Andersen and co-workers, who have optimized the series to improve binding in a lipophilic cleft in PTP1B.[14] To achieve a robust solid-phase methodology that can be used to synthesize individual compounds as well as libraries, we have sought to optimize synthesis through use of the Wang resin. To date, there are few reports of solid-phase synthesis of oxamic acid phosphate mimics. These compounds are typically made using traditional solution-phase synthesis or by tethering onto a remote functionality.

Although Wang resins are commonly used in combinatorial library synthesis, the potential use of oxalyl anchors on Wang resins has not previously been explored. The solid-phase synthesis of oligonucleotides using nucleosides linked to controlled-pore glass or cross-linked polystyrene supports via oxalyl anchor has previously been reported.[25] Gaytán and

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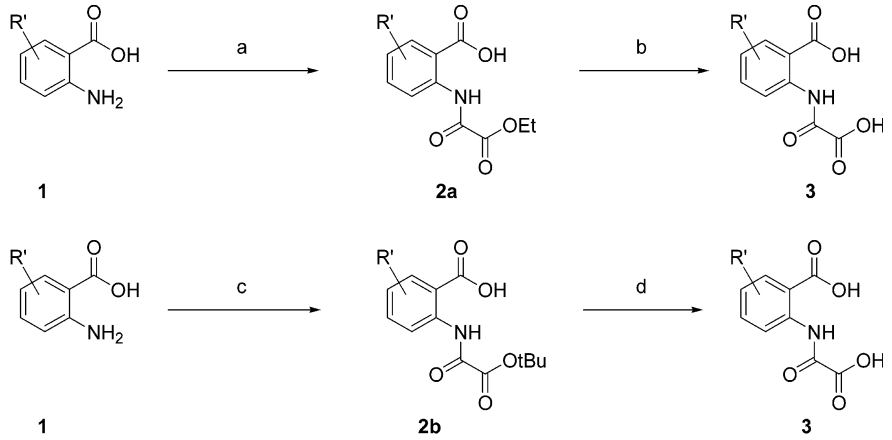

Figure 1. Solution synthesis of 2-(oxalyl-amino)-benzoic acids. Reagents and conditions: (a) ClCOCO(OEt), THF; (b) NaOH; (c) imidazol-1-yl-oxoacetic acid *t*-butyl ester; (d) TFA/DCM.

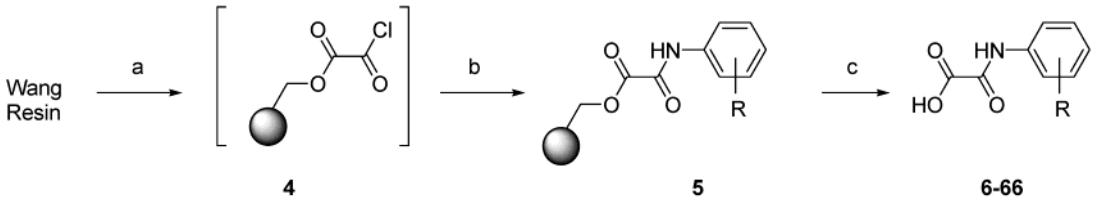

Figure 2. Synthesis of aryl amides of oxalic acid on solid-phase using an oxalyl linker. Reagents and conditions: (a) $(ClCO)_2$, DCM; (b) DIPEA, DCM, $R-C_6H_5-NH_2$; (c) 20% TFA/DCM

Martinez[26] have attached steroids onto solid support by modifying isoargentatin-D with oxalyl chloride and coupling it to LightCycler-Fluorescein long chain alkylamino controlled pore glass (LCAA-CPG) support, following the general conditions of Letsinger[25] for oligonucleotide synthesis on resin. Eritja and co-workers[27] used a similar methodology in their recent synthesis of solid-phase oligonucleotides.

These reports involve the incorporation of oxalyl groups onto the series of interest prior to attachment onto resin or introducing the oxalyl group during the cleavage step from resin. We recognized that an active oxalyl group incorporated onto Wang resin could be used to couple a variety of nucleophiles and create libraries in a quick and efficient manner. We have coupled oxalyl chloride to Wang resin and used the active resin-bound acid chloride as a linker to incorporate aromatic amines to solid phase. Our methodology has the advantage over solution-phase synthesis of ease of use and lack of purification of intermediates. Multifunctionalized aromatic amines can be coupled to the oxalyl anchor without the need for protection/deprotection of functionalities or intermediate purification. We report here the rapid synthesis of a library of monoamides of oxalic acids by reacting aromatic amines to Wang resin-anchored oxalyl chloride.

Results and Discussion

The general synthesis of the 2-(oxalylamino)benzoic acid series[14,15,24,28] is shown below in Figure 1. Treating commercially available anthranilic acid (**1**) derivatives with monoethyl oxalyl chloride yields the desired base-sensitive ethyl oxalyl ester intermediates (**2a**). Alternatively, treatment of (**1**) with imidazol-1-yl-oxoacetic acid *tert*-butyl ester will yield the acid-sensitive *tert*-butyl oxalyl ester intermediate (**2b**). These intermediate esters may precipitate out of solution, but usually require chromatographic purification prior to hydrolysis yielding the desired product (**3**). The *tert*-butyl or ethyl intermediate esters are hydrolyzed with acid or base, respectively.

We have developed a more direct route to this series utilizing solid-phase chemistry. The generation of these desired products without the need for purification makes our approach feasible for rapid generation of libraries as well as for monomer synthesis. Our approach involves acylation of the Wang resin with excess oxalyl chloride in dichloromethane to yield a novel resin-bound reactive acyl halide **4** (Figure 2). The reaction may be performed without inert reaction conditions or the use of freshly distilled dry solvent. Excess reagent may be removed by washing the resin with chlorinated solvent. This active linker undergoes facile reactions with various arylamines in chlorinated solvents to form the coupled resin-bound product. Aromatic amines were used to yield the desired products, shown in Table 1. Most of the aromatic amines were soluble in dichloromethane and base. *N*,*N*-Diisopropylethylamine (DIPEA) or triethylamine (TEA) were used as the base in the reaction. In some cases, a small amount of DMSO was added to the reaction solution to solubilize the aromatic amines. After allowing the reaction to shake for several hours, the products were cleaved from the resin with TFA/DCM.

This methodology can be used for the generation of 96-member libraries using Robbins blocks (60-mmol scale, 2.4-mL volume), as well as for monomer synthesis using polypropylene tubes (150−230 mmol scale, 20 mL volume). Sixty compounds were produced in parallel using this methodology (Table 1). Each entry consists of the desired product, its molecular weight, the purity of the desired

Table 1. Monoamides of Oxalic Acid Synthesized on Solid-Phase Wang Resin Using Oxalyl Chloride-Containing Linker

compd	name	MW	purity (LC/MS) of reaction (%)	crude yield (by mass, %)	t_R
6	2-(oxalylamino)benzoic acid	209.16	100	69	0.41
7	3-methoxy-2-(oxalylamino)benzoic acid	239.18	91	46	0.42[c]
8	5-methoxy-2-(oxalylamino)benzoic acid	239.18	100	29	0.67[c]
9	3-methyl-2-(oxalylamino)benzoic acid	223.18	100	66	0.42[c]
10	4-methyl-2-(oxalylamino)benzoic acid	223.18	100	51	0.85[c]
11	5-methyl-2-(oxalylamino)benzoic acid	223.18	100	12	0.85[c]
12	2-methyl-6-(oxalylamino)benzoic acid	223.18	100	64	0.45[c]
13	4,5-dimethoxy-2-(oxalylamino)benzoic acid	269.21	100	91	0.38
14	3-hydroxy-2-(oxalylamino)benzoic acid	225.15	50	71	ND[d]
15	5-hydroxy-2-(oxalylamino)benzoic acid	225.15	100	55	0.29
16	4-nitro-2-(oxalylamino)benzoic acid	254.15	100	55	0.51
17	5-nitro-2-(oxalylamino)benzoic acid	254.15	100	70	0.36
18	3,5-diiodo-2-(oxalylamino)benzoic acid	460.95	50	67	0.84
19	5-bromo-2-(oxalylamino)benzoic acid	288.05	100	69	0.75
20	3,5-dibromo-2-(oxalylamino)benzoic acid	366.95	93	56	0.49
21	3,5-dibromo-2-chloro-6-(oxalylamino)benzoic acid	401.39	100	61	0.38
22	3-chloro-2-(oxalylamino)benzoic acid	243.6	100	67	0.46
23	4-chloro-2-(oxalylamino)benzoic acid	243.6	100	74	0.73
24	5-chloro-2-(oxalylamino)benzoic acid	243.6	96	74	0.79
25	2-chloro-6-(oxalylamino)benzoic acid	243.6	100	74	0.34
26	3,5-dichloro-2-(oxalylamino)benzoic acid	278.05	100	68	0.62
27	3,6-dichloro-2-(oxalylamino)benzoic acid	278.05	100	74	0.27
28	4-fluoro-2-(oxalylamino)benzoic acid	227.15	100	78	0.38
29	5-fluoro-2-(oxalylamino)benzoic acid	227.15	100	79	0.65
30	2-fluoro-6-(oxalylamino)benzoic acid	227.15	100	58	0.5
31	4,5-difluoro-2-(oxalylamino)benzoic acid	245.14	94	77	0.45
32	3,5-dibromo-2-fluoro-6-(oxalylamino)benzoic acid	384.94	100	97	0.56
33	5-iiodo-2-(oxalylamino)benzoic acid	335.05	100	72	0.92
34	3-(oxalylamino)phthalic acid	253.17	85	68	0.27
35	2-(oxalylamino)terephthalic acid	253.17	100	63	0.35
36	2-(oxalylamino)terephthalic acid 1-methyl ester	267.19	100	52	0.39
37	3-(oxalylamino)isonicotinic acid	210.14	100	74	0.24
38	3-(oxalylamino)1*H*-pyrazole-4-carboxylic acid	199.12	93	73	0.26
39	3-(oxalylamino)pyrazine-2-carboxylic acid	211.13	100	76	0.24
40	2-(oxalylamino)nicotinic acid	210.14	*e*	20	ND[d]
41	2-ethylsulfanyl-4-(oxalylamino)pyrimidine-5-carboxylic acid	271.25	40[e]	47	0.45
42	2-methyl-3-(oxalylamino)quinoline-4-carboxylic acid	274.23	100	36	0.27
43	4-benzenesulfonyl-3-(oxalylamino)thiophene-2-carboxylic acid	355.34	100	47	0.3
44	3-(oxalylamino)-4-(propane-2-sulfonyl)thiophene-2-carboxylic acid	321.33	100	50	0.31
45	5-methylsulfanyl-3-(oxalylamino)-4-(propane-2-sulfonyl)thiophene-2-carboxylic acid	367.42	40[e]	42	ND[d]
46	5-(oxalylamino)−2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid	243.13	10[e]	46	ND[d]
47	*N*-(2-carbamoyl-phenyl)oxalamic acid	208.17	100	66	0.33
48	3-(oxalylamino)naphthalene-2-carboxylic acid	259.21	100	60	0.87
49	*N*-(4-methoxyphenyl)oxalamic acid	195.17	100	61	0.58
50	*N*-(2,6-dichloro-4-cyanophenyl)oxalamic acid	259.05	85	41	0.35
51	*N*-(2-methoxy-5-trifluoromethyl-phenyl)oxalamic acid	263.17	96	33	1.01
52	*N*-(2-methyl-3-nitrophenyl)oxalamic acid	224.17	97	28	0.37
53	*N*-(4-phenoxyphenyl)oxalamic acid	257.24	97	37	1.04
54	*N*-(3,4-dimethyl-phenyl)oxalamic acid	193.2	88	42	0.77
55	*N*-(3-phenoxyphenyl)oxalamic acid	257.24	82	26	1.03
56	*N*-(4-ethoxyphenyl)oxalamic acid	209.2	89	42	0.82
57	*N*-(4-cyanomethyl-phenyl)oxalamic acid	204.18	100	41	0.38
58	*N*-(2-methoxy-6-methyl-4-nitrophenyl)oxalamic acid	254.2	100	18	ND[d]
59	*N*-(4-bromo-2-fluorophenyl)oxalamic acid	262.03	100	17	0.74
60	*N*-(2,6-diethyl-phenyl)oxalamic acid	221.25	84	35	0.8
61	*N*-(4-*sec*-butyl-phenyl)oxalamic acid	221.25	83	23	1.2
62	*N*-(4-bromo-2-ethyl-phenyl)oxalamic acid	272.10	80	22	0.97
63	*N*-(3-fluoro-4-methoxyphenyl)oxalamic acid	213.16	88	55	0.48
64	*N*-(4-butoxyphenyl)oxalamic acid	237.25	80	53	1.13
65	*N*-(4-propyl-phenyl)oxalamic acid	207.23	100	35	1.06
66	*N*-(4-pentyloxyphenyl)oxalamic acid	251.28	89	27	1.31

[a] The purity was determined by LC/MS. [b] The retention times were recorded on a Waters MUX system, unless otherwise noted. [c] Finnigan LC/MS/ [d] No data/ [e] Insoluble starting material.

product, the unoptimized yield, and the t_R value as revealed by LC/MS. We examined the scope and limitations of the solid-phase reaction. Aromatic amines with multiple nucleophilic functionality, such as diamines, were not used in this library. A broad range of aromatic amines reacted with the resin bound acid chloride. Aromatic amines containing electron-donating groups, as well as electron-withdrawing groups successfully produced the desired products. Thus, both 2-amino-4,5-dimethoxybenzoic acid and 2-amino-4-chlorobenzoic acid produce the desired products **13** and **23**, respectively, in high yield and purity. Other aromatic analogues, such as pyrazole (**38**), pyrazine (**39**), thiophene

(**43** and **44**) and naphthalene (**48**) systems, react equally well. An important factor was the solubility of the amines in solvents that would not react with the labile resin-bound acid chloride. In a few cases in which it appeared the amine was poorly soluble in chlorinated solvents, a few drops of DMSO were added to the reaction mixture.

In summary, 60 aromatic amines (Table 1) were reacted with resin-bound oxalyl chloride. Desired products were obtained in high purity, with unoptimized yields up to 97%. We did try to avoid entries that contained additional nucleophilic functionality (such as multiple amines or hydroxyl groups) in the starting material which might react with the resin and cause competitive reactions. For example, entries **14** and **15**, which contained nucleophilic hydroxyl groups, gave low purity and low yield, respectively. In the case of the diiodo derivative, entry **18**, we saw mixtures of desired product as well as the monoiodo analogue. There were only a few cases in which the weak nucleophilicity of the starting material amine as well as perhaps steric hindrance caused the reaction to fail or give poor yields. Substituted aromatic derivatives that contained additional steric bulk or electron-withdrawing groups, such as bromine, entry **59**, tended to lower the overall yield. The desired product was formed on resin, and the purity after cleavage reflects the success of our method. It was also noted that starting materials that were poorly soluble in chlorinated solvents (such as nicotinic acid derivative **40** and pyrimidine derivatives **41** and **46**) were problematic in the solid-phase reaction, yielding little or no desired products. We have observed that the sensitive resin-bound acid chloride must be used immediately upon generation. Prolonged exposure of the dry resin-bound acid chloride produces a marked decrease in the yield of desired products. The purity of the library was assessed by LC/MS. In general, the series did not ionize well in the mass spectrometer, and both electrospray positive and electrospray negative spectra were obtained for most compounds. ^{1}H NMR spectra were obtained for select compounds.

Experimental Section

Materials were obtained from commercial suppliers and were used as received. The dichloromethane used in the synthesis was reagent grade Fisher brand. Wang resin was purchased from Advanced ChemTech. ^{1}H NMR spectra were measured on a Varian AM300 spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as the internal standard. LC/MS data were recorded on a Waters ZQ electrospray mass spectrometer equipped with 4-channel MUX capabilities (Milford, MA) with ELS detection using a Princeton SPHER HTS 60 Å, 5-μm column (3 × 50 mm) (Princeton Chromatography, Cranbury, NJ). Typical gradients were 25−100% CH_3CN/H_2O containing 0.1% formic acid and 0.01% TFA, 2.25 min, flow rate 1.5 mL/min. The solid-phase reactions were performed in 96-well Robbins blocks (2 mL/well) as well as in polypropylene tubes. A typical procedure using 20-mL polypropylene BioRad tubes is presented.

General Procedure for Synthesis of Monoamides of Oxalic Acid. To 150 mmol of Wang resin preswollen in dichloromethane was added 10 equiv of 2 M oxalyl chloride in dichloromethane. The reaction was shaken at room temperature for 4 h. The resin was filtered and washed thrice with 50 mL of dichloromethane, and the procedure was repeated once more to ensure maximum loading of the resin. The resulting activated acid chloride tethered to the Wang resin was immediately used in the subsequent coupling reaction. A predissolved solution of anthranilic acid (5 equiv) in 3 mL of dichloromethane and DIPEA (5 equiv) was added to the resin in 5 mL dichloromethane. The solution was shaken for 5 h. After sequential filtration and washing of the resin with aliquots of methanol and dichloromethane, a solution of 20% acetic acid in dichloromethane was added, and the resin was shaken for 10 min and then filtered. An acidic workup is required to remove excess base, which may have bound to acidic groups on the resin. Specifically, when anthranilic acids were used as starting materials, this step was necessary. Cleavage from the resin using TFA/DCM (1:1) gave the desired oxalic acid monoamide as a solid. In some cases, a trace amount of *N*,*N*-diisopropylethylamine/trifluoroacetic acid salt was present, as evidenced by ^{1}H NMR. The salt was quantitatively removed by dissolving the product in 10% acetic acid in methanol and passing through a SCX ion exchange column. The solvent was removed in vacuo to yield the desired product.

2-(Oxalylamino)benzoic Acid (6). ^{1}H NMR (300 MHz, CD3OD): δ 8.72 (d, J = 7.9 Hz, 1H), 8.14 (dd, J = 1.6, 7.9 Hz, 1H), 7.62−7.59 (m, 1H), 7.26−7.21 (m, 1H). ELS LC/MS *m*/*z*: MH^- 208.26.

3-Methoxy-2-(oxalylamino)benzoic Acid (7). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.92 (br s, 1H), 10.03 (s, 1H), 7.38−7.31 (m, 3H), 3.82 (s, 3H). ELS LC/MS *m*/*z*: MH^+ 240.38.

5-Methoxy-2-(oxalylamino)benzoic Acid (8). ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.92 (br s, 1H), 12.25 (s, 1H), 8.55 (d, J = 9.2 Hz, 1H), 7.52 (d, J = 3.0 Hz, 1H), 7.29 (dd, J = 3.0, 9.2 Hz, 1H), 2.50 (s, 3H). ELS LC/MS *m*/*z*: MH^+ 240.40.

3-Methyl-2-(oxalylamino)benzoic Acid (9). ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.02 (br s, 1H), 10.45 (s, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 2.21 (s, 3H). ELS LC/MS *m*/*z*: MH^+ 224.05.

4-Methyl-2-(oxalylamino)benzoic Acid (10). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.51 (s, 1H), 8.48 (d, J = 1.1 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.05 (dd, J = 1.1, 7.9 Hz, 1H), 2.34 (s, 3H). ELS LC/MS *m*/*z*: MH^+ 224.40.

5-Methyl-2-(oxalylamino)benzoic Acid (11). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.40 (s, 1H), 8.52 (d, J = 8.6 Hz, 1H), 7.85 (d, J = 0.9 Hz, 1H), 7.48 (dd, J = 0.9, 8.6 Hz, 1H), 2.33 (s, 3H). ELS LC/MS *m*/*z*: MH^+ 224.38.

2-Methyl-6-(oxalylamino)benzoic Acid (12). ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.95 (br s, 1H), 10.96 (s, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 2.43 (s, 3H). ELS LC/MS *m*/*z*: MH^+ 224.40.

4,5-Dimethoxy-2-(oxalylamino)benzoic Acid (13). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.55 (s, 1H), 8.65 (br s,

1H), 8.39 (s, 1H), 7.48 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H). ELS LC/MS *m/z*: MH^- 268.32, MH^+ 270.33.

5-Hydroxy-2-(oxalylamino)benzoic Acid (15). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.21 (br s, 1H), 9.79 (br s, 1H), 8.45 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 3.0 Hz, 1H), 7.07 (dd, J = 3.0, 8.8 Hz, 1H). ELS LC/MS *m/z*: MH^+ 224.40. ELS LC/MS *m/z*: $[MH + 18]^+$ 244.32.

5-Nitro-2-(oxalylamino)benzoic Acid (17). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.82 (s, 1H), 8.83 (d, J = 9.2 Hz, 1H), 8.77 (d, J = 3.0 Hz, 1H), 8.53 (dd, J = 3.0, 9.2 Hz, 1H). ELS LC/MS *m/z*: MH^- 253.23.

5-Bromo-2-(oxalylamino)benzoic Acid (19). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.45 (s, 1H), 8.57 (d, J = 8.9 Hz, 1H), 8.12 (d, J = 2.3 Hz, 1H), 7.87 (dd, J = 2.3, 8.9 Hz, 1H). ELS LC/MS *m/z*: MH^+ 288.16.

3,5-Dibromo-2-(oxalylamino)benzoic Acid (20). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.60 (br s, 1H), 8.21 (d, J = 2.3 Hz, 1H), 8.20 (d, J = 2.3 Hz, 1H). ELS LC/MS *m/z*: MH^- 364.03.

3,5-Dibromo-2-chloro-6-(oxalylamino)benzoic Acid (21). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.86 (br s, 1H), 8.32 (s, 1H). ELS LC/MS *m/z*: MH^- 398.00.

3-Chloro-2-(oxalylamino)benzoic Acid (22). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.58 (s, 1H), 7.80 (dd, J = 1.3, 7.6 Hz, 1H), 7.77 (dd, J = 1.3, 7.9 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H). ELS LC/MS *m/z*: MH^- 242.26, MH^+ 244.26.

4-Chloro-2-(oxalylamino)benzoic Acid (23). ^{1}H NMR (300 MHz, DMSO-d_6): δ 14.2 (bs, 1H), 12.58 (s, 1H), 8.69 (d, J = 2.3 Hz, 1H) 8.05 (d, J = 8.6 Hz, 1H), 7.33 (dd, J = 2.3, 8.6 Hz, 1H). ELS LC/MS *m/z*: MH^- 242.27, MH^+ 244.27.

5-Chloro-2-(oxalylamino)benzoic Acid (24). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.44 (s, 1H), 8.63 (d, J = 9.2 Hz, 1H) 7.99 (d, J = 2.6 Hz, 1H), 7.75 (dd, J = 2.6, 9.2 Hz, 1H). ELS LC/MS *m/z*: MH^- 242.21, MH^+ 244.29.

2-Chloro-6-(oxalylamino)benzoic Acid (25). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.56 (s, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 8.2 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H). ELS LC/MS *m/z*: MH^- 242.28.

3,5-Dichloro-2-(oxalylamino)benzoic Acid (26). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.63 (s, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H). ELS LC/MS *m/z*: MH^- 276.18.

3,6-Dichloro-2-(oxalylamino)benzoic Acid (27). ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.89 (br s, 1H), 10.80 (s, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.58 (d, J = 8.9 Hz, 1H). ELS LC/MS *m/z*: MH^- 276.16.

4-Fluoro-2-(oxalylamino)benzoic Acid (28). ^{1}H NMR (300 MHz, DMSO-d_6): δ 14.05 (br s, 1H), 12.67 (s, 1H), 8.43 (dd, J = 1.9, 2.6 Hz, 1H), 8.13 (dd, J = 6.6, 8.9 Hz, 1H), 7.15−7.08 (m, 1H). ELS LC/MS *m/z*: MH^- 226.30, MH^+ 228.32.

5-Fluoro-2-(oxalylamino)benzoic Acid (29). ^{1}H NMR (300 MHz, DMSO-d_6): δ 14.20 (br s, 1H), 12.38 (s, 1H), 8.64 (dd, J = 5.3, 9.2 Hz, 1H), 7.79−7.75 (m, 1H), 7.61−7.54 (m, 1H). ELS LC/MS *m/z*: MH^- 226.27, MH^+ 228.32.

2-Fluoro-6-(oxalylamino)benzoic Acid (30). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.69 (br s, 1H), 8.18 (d, J = 8.2 Hz, 1H), 7.67−7.59 (m, 1H), 7.17−7.10 (m, 1H). ELS LC/MS *m/z*: MH^- 226.33, MH^+ 228.30.

4,5-Difluoro-2-(oxalylamino)benzoic Acid (31). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.54 (s, 1H), 8.61 (dd, J = 7.6, 13.5 Hz, 1H), 8.03 (dd, J = 9.2, 11.2 Hz, 1H). ELS LC/MS *m/z*: MH^- 244.24, MH^+ 246.32.

3,5-Dibromo-2-fluoro-6-(oxalylamino)benzoic Acid (32). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.80 (br s, 1H), 8.31 (d, J = 6.9 Hz, 1H). ELS LC/MS *m/z*: MH^- 383.99.

5-Iodo-2-(oxalylamino)benzoic Acid (33). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.44 (br s, 1H), 8.43 (d, J = 8.9 Hz), 8.29 (d, J = 2.3 Hz, 1H), 8.00 (dd, J = 2.3, 8.9 Hz, 1H). ELS LC/MS *m/z*: MH^- 334.09, MH^+ 336.20.

2-(Oxalylamino)terephthalic Acid 1-Methyl Ester (36). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.18 (s, 1H), 9.15 (d, J = 1.6 Hz), 8.14 (d, J = 8.2 Hz, 1H), 7.80 (dd, J = 1.6, 8.2 Hz, 1H), 3.88 (s, 3H). ELS LC/MS *m/z*: MH^+ 268.34.

3-(Oxalylamino)-1*H*-pyrazole-4-carboxylic Acid (38). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.72 (s, 1H), 8.06 (s, 1H). ELS LC/MS *m/z*: MH^+ 200.35.

***N*-(2-Carbamoylphenyl)oxalamic Acid (47).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.91 (s, 1H), 8.55 (d, J = 8.2 Hz, 1H), 8.33 (s, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.78 (s, 1H), 7.55−7.60 (m, 1H), 7.20−7.25 (m, 1H). ELS LC/MS *m/z*: MH^- 207.19, MH^+ 209.39.

3-(Oxalylamino)naphthalene-2-carboxylic Acid (48). ^{1}H NMR (300 MHz, DMSO-d_6): δ 14.05 (br s, 1H), 12.28 (s, 1H), 9.08 (s, 1H), 8.77 (s, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.64−7.69 (m, 1H), 7.52−7.57 (m, 1H). ELS LC/MS *m/z*: MH^- 258.27.

***N*-(4-Methoxyphenyl)oxalamic Acid (49).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.62 (s, 1H), 7.69 (d, J = 8.9 Hz, 1H), 6.92 (d, J = 8.9 Hz, 1H), 3.76 (s, 3H). ELS LC/MS *m/z*: MH^- 194.29, MH^+ 196.34.

Conclusion

We have presented the use of a linker to synthesize aromatic monoamides of oxalic acids in a fast and efficient manner on solid-phase. We have shown that our methodology works with Wang resin as the solid phase and can thus be useful for the synthesis of individual compounds as well as for library synthesis. Resin-bound oxalyl chloride can react with a variety of nucleophiles. Both activated and deactivated amines successfully couple to the linker and upon cleavage yield the desired products. This method is useful for the synthesis of libraries and can also be used for generation of the single products without any purification steps.

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Supporting Information Available. ^{1}H NMR spectra with internal standards and ELS LC/MS traces are included for each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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