Synthetic Communications®, 35: 1567–1575, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200061542

Taylor & Francis
Taylor & Francis Group

Use of Oligosalicylates in the Preparation of Phenolic Amido Acids

David Gschneidner, JoAnne Corvino, John Freeman, Doris O'Toole, Lynn Shields, and Eric Wang
Emisphere Technologies Inc., Tarrytown, New York, USA

Abstract: A simplified methodology has been developed for preparing salicylamides from the corresponding acids via oligosalicylates which both protect the phenolic group and, at the same time, activate the carboxyl for coupling.

Keywords: Amide coupling, activated ester, salicylamide, oligomer

INTRODUCTION

The reaction of an amine with a carboxylic acid derivative to form an amide is well-known chemistry,[1] and numerous methods of amide preparation have been reported.[2] The most straightforward synthesis of amides is the acylative coupling of an amine with an acid chloride.[1] The reaction is often complicated by unwanted side reactions, particularly when other functional groups are present. Additionally, acid chlorides are corrosive and moisture sensitive, and can be difficult to use on a large scale. In many cases, the acid chlorides are not commercially available and must be prepared from their more readily available acid precursors. Taken together, these issues have created the need for alternative, uncomplicated amide syntheses.

The synthesis of phenolic amido acids (see Fig. 1) from acid chlorides represents a difficult challenge. When the phenolic group is left unprotected, the yields are typically low and by-products are produced that make purification complicated. For this reason, it is preferable to protect the phenol before making the acid chloride. The protected acid chloride can be used

Received in the USA February 11, 2005
Address correspondence to David Gschneidner, Emisphere Technologies Inc., 785 Old Saw Mill River Road, Tarrytown, NY 10591, USA. E-mail: dgschnei@emisphere.com

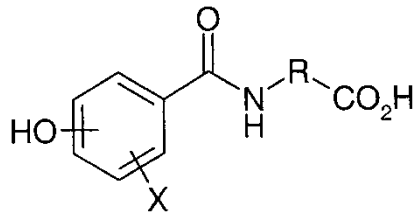
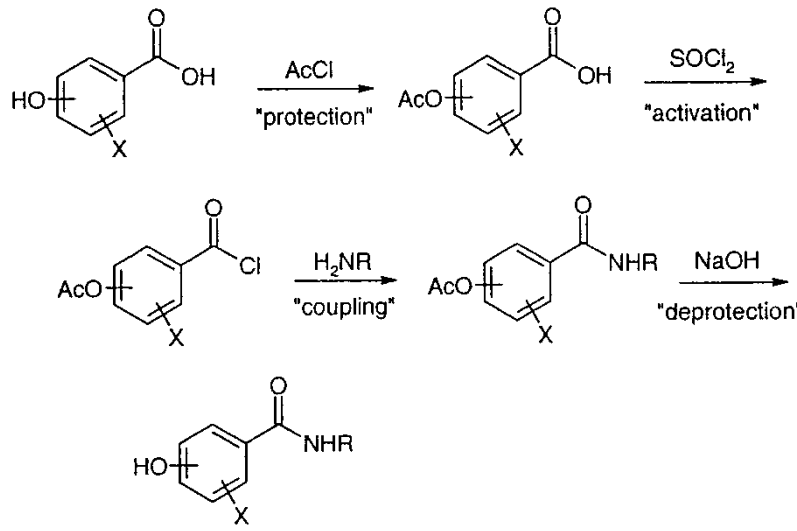


Figure 1. Genetic structure of a phenolic amido acid.

for coupling with an amine. This process then requires a subsequent deprotection step (see Scheme 1). In many cases, the protecting group is often a reactive moiety, such as an acetate, and can be the source of by-product formation. Finally, the coupling reaction is often most conveniently conducted in an aqueous medium (Schotten–Baumann conditions). These conditions result in lower yields of the desired amide because of competitive and unselective hydrolysis of the acid chloride by the solvent. In our hands, typical overall yields for the four-step process are around 40%.

RESULTS AND DISCUSSION

As part of our program to prepare oral drug-delivery agents that have phenolic amide functionality, a simpler, more efficient synthetic route to these compounds was needed. Thus, we sought a general procedure for coupling

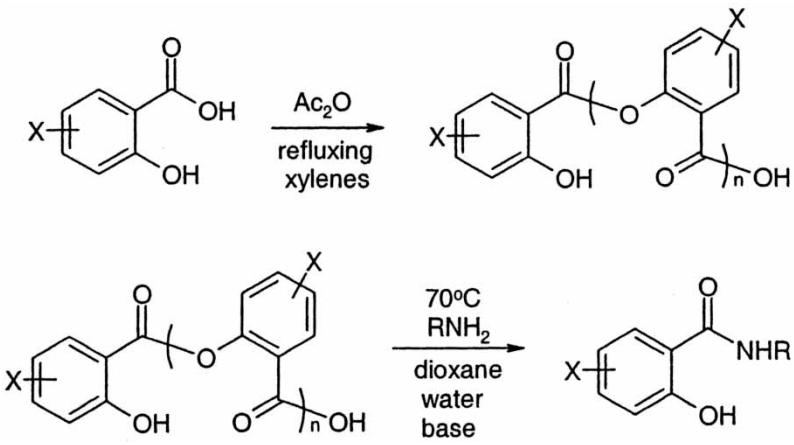


Scheme 1.

phenolic esters, especially those bearing electron-withdrawing groups (EWG) on the aryl ring, with amines. For the reasons discussed previously and because phenolic esters are active electrophiles,[3] we decided to examine oligomeric salicylates as coupling agents for the preparation of phenolic amido acids. This methodology combines the two-step protection and activation sequence into a single synthetic step. Similarly, the coupling and deprotection steps are also combined. Thus, the use of oligosalicylate coupling agents efficiently transforms a four-step procedure into a two-step procedure.

The overall process is shown in Scheme 2. Polymerization of salicylic acid is a well-known reaction.[4] In the present study, we found that low-molecular-weight oligomers are preferred because they are more soluble than higher polymers in organic aprotic polar solvents such as dioxane. The oligosalicylates were prepared by heating the salicylic acid in xylenes in the presence of acetic anhydride. The volatiles were distilled to a final temperature of 190–200°C. Acetic acid production continues throughout the oligomerization process. The desired oligomer was isolated by either pouring into a tray to form a glass or by charging the molten oligomer directly to the coupling reaction solvent (dioxane or 1,2-dimethoxyethane).

Amide bond formation can be accomplished by adding an aqueous solution of the amino acid containing a slight excess of base to the oligomer solution. The base, sodium hydroxide or potassium carbonate, is required when the amine contains acid groups. For simple amines, no added base is needed. In general, the reactions are complete after heating for 3–6 h at 70°C. The reaction is readily followed by high-pressure liquid chromatography (HPLC). The reactions are clean and, in most cases, the only by-product is salicylic acid. Pure products are easily obtained by exploiting



Scheme 2.

the pK_a differences between aliphatic acids and salicylic acids (about 1.8 pH units) and/or recrystallization.

A representative oligosalicylate chromatogram is shown in Fig. 2a for oligosalicylate. The numerous peaks represent the various molecular-weight oligomer components. As the reaction proceeds, two distinct peaks replace the complicated oligosalicylate HPLC profile. At the completion of the reaction only these two new components remain, the desired amide **1** and the salicylic acid by-product (Fig. 2b).

Table 1 shows results using various substrates (the yields quoted are unoptimized). In general, the procedure works best with aliphatic amines. Aromatic amines, however, do not appear to be sufficiently reactive to give good product yields (Entry 13), unless the oligosalicylate is further activated by additional EWGs on the aromatic ring (Entry 14).

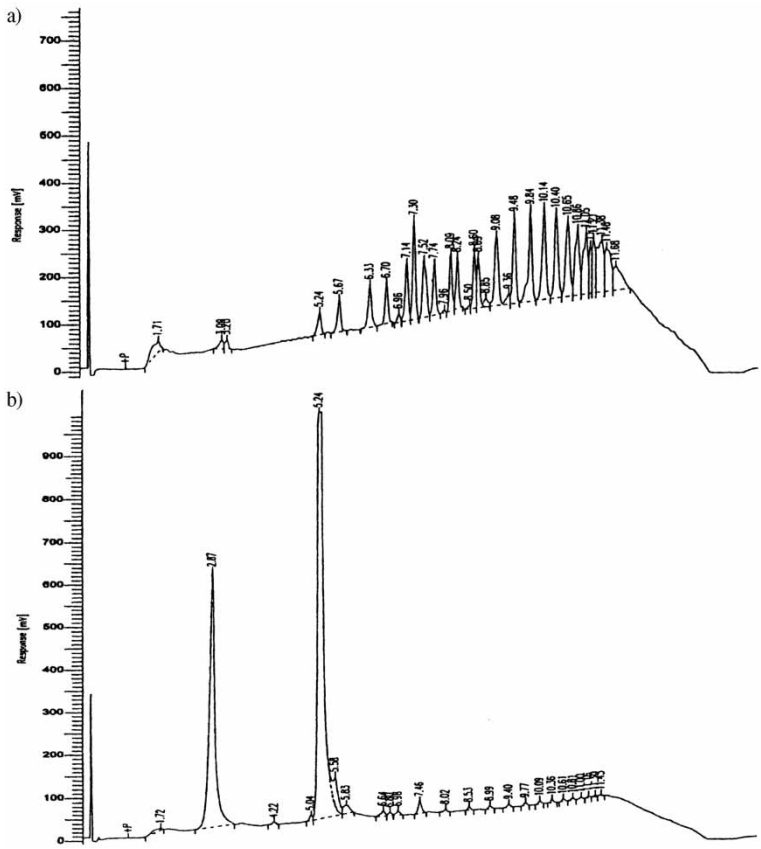
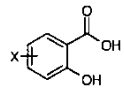
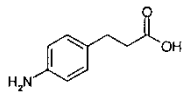
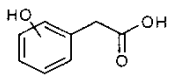
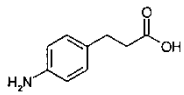


Figure 2. (top) HPLC trace of oligosalicylate, (bottom) HPLC trace following reaction with amine. The peak on the left is salicylic acid and the peak on the right is product.

Table 1. Amination of oligosalicylates with aminoacids

Entry	Phenolic Acid	Amine	Yield[a] (%)
			
1	X = H	8-aminocaprylic acid	74
2	X = 3-Me	8-aminocaprylic acid	41
3	X = 4-Me	8-aminocaprylic acid	71
4	X = 5-Cl	8-aminocaprylic acid	44
5	X = 5-Br	8-aminocaprylic acid	59
6	X = 3,5-diF	8-aminocaprylic acid	56
7	X = 3-F, 5-Cl	8-aminocaprylic acid	51
8	X = 3-Cl, 5-F	8-aminocaprylic acid	53
9	X = 4-OMe	4-aminobutyric acid	47
10	X = 4-OMe	10-aminodecanoic acid	32
11	X = 3,5-diCl	11-aminoundecanoic acid	47
12	X = 3,5-diCl	10-aminodecanoic acid	20
13	X = H		0
14	X = 3,5-diCl		46
			
15	4 = OH	8-aminocaprylic acid	12
16	3 = OH	8-aminocaprylic acid	10

[a]Yields are for recrystallized products.

Overall, the reaction works well with a variety of substituted salicylic acid oligomers. Both electron-withdrawing and electron-donating groups are well tolerated. In addition, nonconjugated carboxylic acid oligomers give significantly lower yields, probably because of their inability to act as good leaving groups (Entries 15 and 16).

CONCLUSION

In summary, the use of oligosalicylate coupling reagents to prepare phenolic amido acids represents a novel and useful synthetic methodology. This chemistry facilitates amide bond formation in which the protection of the hydroxyl group is incorporated into the activation procedure, and, similarly,

deprotection is an inherent part of the coupling reaction. Additionally, this reaction sequence avoids the use of corrosive and difficult-to-handle acid chloride reagents. This procedure using oligosalicylates as coupling agents is a simple, straightforward method for the preparation of amides.

EXPERIMENTAL

General

Melting points are uncorrected. NMR spectra were measured using a Bruker AM300 (300 MHz) spectrometer. ^{1}H chemical shifts are reported in δ ppm relative to dimethylsulfoxide (DMSO) as an internal standard. Reverse-phase HPLC was performed with a Vydac Protein and Peptide (C_{18}, 250 × 4.6 mm, 5 μm particle size, 300 A pore size) column and a UV detector (220 nm). The sample was eluted with 0.1% trifluoroacetic acid (TFA) in water (mobile phase A) and a 0.1% TFA in 50% acetonitrile/water (mobile phase B) (flow rate, 1 mL/min; gradient, 0% to 100% B over 20 min and 100% B throughout). Microanalytical data was obtained from Robertson Microlit Laboratory, Inc. (Madison, NJ). All starting materials were purchased from commercial sources and used without further purification.

Preparation of Oligosalicylate. Acetic anhydride (14.50 mL, 15.69 g, 0.154 mol, 1.02 eq), salicylic acid (20.79 g, 0.151 mol, 1.00 eq), and xylenes (60 mL) were added to a 250-mL, three-neck flask fitted with a magnetic stir bar, a thermometer, and a Dean–Stark trap with condenser. The flask was placed in a sand bath and heating of the cloudy white mixture began. The reaction mixture became a clear solution around 100°C. Most of the volatile organics (xylenes and acetic acid) were distilled into the Dean–Stark trap over three hours (135–146°C). Distillation was continued for another hour (a total of 75 mL distilled), during which the pot temperature slowly rose to 195°C and the distillate slowed to a trickle. The residue was poured off while still hot into an aluminum tray. Upon cooling, a brittle yellow glass formed. The solid was ground to a fine powder. The 18.95 g of oligosalicylate produced was used without further purification.

Preparation of N-(salicyloyl)-8-aminocaprylic Acid (1). A solution of 4.96 g (17.9 mmol, 1.19 eq) of a 50% (by weight) aqueous potassium carbonate, 2.39 g of 8-aminocaprylic acid (15.0 mmol, 1.00 eq), and water (3 mL) were charged to a 250-mL, round-bottom flask equipped with a magnetic stir bar and an addition funnel. The white cloudy mixture was treated with a solution of oligosalicylate (2.44 g, 20.2 mmol 1.35 eq) and dioxane (40 mL), added over 3 min. The addition funnel was replaced with a condenser, and the reaction mixture was heated to 90°C for 4 h (at which time the reaction was determined to have finished, by HPLC). The clear orange reaction mixture was cooled to 40°C, filtered, and acidified to

pH = 1 with 3% (by weight) aqueous hydrochloric acid. The mixture was concentrated in vacuo (60°C, 50 mm) to remove all the dioxane and some of the water. The solid (which precipitated from solution during stripping) was isolated by filtration while still warm. The light pink solid was recrystallized from 70 mL of 65% ethanol/water. The solid was recovered by filtration and was dried over 18 h in a 50°C vacuum oven. The N-(salicyloyl)-8-aminocaprylic acid was isolated as a white solid (3.11 g, 74%), mp 117–8°C; ^{1}H NMR (DMSO-d_6) δ 12.75 (s, 1H), 12.00 (s 1H), 8.80 (t, 1H), 7.83 (dd, 1H), 7.38 (td, 1H), 6.87 (m, 2H), 3.27 (q, 2H), 2.19 (t, 2H), 1.51 (m, 4H), 1.29 (m, 6H). Anal. calcd. for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.44; H, 7.54; N, 5.00.

The following compounds were similarly prepared from the corresponding carboxylic acids and amines:

Preparation of N-(3-methylsalicyloyl)-8-aminocaprylic Acid (2). Mp 88–90°C, ^{1}H NMR (DMSO-d_6) δ 13.3 (s, 1H), 12.0 (s, 1H), 8.8 (t, 1H), 7.66 (d, 1H), 7.28 (d, 1H), 6.76 (t, 1H), 3.26 (m, 2H), 2.2 (m, 6H), 1.5 (m, 4H), 1.28 (s, 2H). Anal. calcd. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.44; H, 8.02; N, 4.56.

Preparation of N-(4-methylsalicyloyl)-8-aminocaprylic Acid (3). Mp 112–114°C; ^{1}H NMR (DMSO-d_6) δ 12.8 (s, 1H), 12.0 (s, 1H), 8.7 (t, 1H), 7.7 (d, 1H), 6.6 (d, 2H), 3.2 (q, 2H), 2.28 (s, 3H), 2.18 (t, 2H), 1.46 (m, 4H), 1.28 (s, 6H). Anal. calcd. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.66; H, 7.85; N, 4.69.

Preparation of N-(5-chlorosalicyloyl)-8-aminocaprylic Acid (4). Mp 125–158°C; ^{1}H NMR (DMSO-d_6) δ 12.0 (s, 1H), 8.8 (m, 1H), 7.95 (m, 1H), 7.42 (9, 1H), 6.93 (d, 1H), 3.29 (q, 2H), 2.2 (t, 2H), 1.5 (m, 4H), 1.29 (s, 6H). Anal. calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42; N, 4.46. Found C, 57.46; H, 6.28; N, 4.42.

Preparation of N-(5-bromosalicyloyl)-8-aminocaprylic Acid (5). Mp 125–128°C; ^{1}H NMR (DMSO-d_6) δ 12.8 (s, 1H), 12.0 (s, 1H), 8.8 (t, 1H), 8.05 (d, 1H), 7.55 (9, 1H), 6.88 (d, 1H), 3.28 (q, 2H), 2.2 (t, 2H), 1.49 (m, 4H), 1.28 (s, 6H). Anal. calcd. for $C_{15}H_{20}BrNO_4$: C, 50.29; H, 5.63; N, 3.91. Found: C, 50.48; H, 5.71; N, 3.61.

Preparation of N-(3,5-difluorosalicyloyl)-8-aminocaprylic Acid (6). Mp 109–110°C; ^{1}H NMR (DMSO-d_6) δ 13.3 (s, 1H), 12.0 (s, 1H), 9.0 (t, 1H), 7.65 (m, 1H), 7.55 (m, 1H), 3.3 (q, 2H), 2.2 (t, 2H), 1.5 (m, 4H), 1.25 (s, 6H). Anal. calcd. for $C_{15}H_{19}F_2NO_4$: C, 57.14; H, 6.07; N, 4.44. Found: C, 57.3; H, 6.40; N, 4.43.

Preparation of N-(3-fluoro-5-chlorosalicyloyl)-8-aminocaprylic Acid (7). Mp 108–109°C; ^{1}H NMR (DMSO-d_6) (s, 1H), 12.0 (s, 1H), 9.05 (s, 1H), 7.8 (q, 1H), 7.65 (q, 1H), 3.3 (q, 2H), 2.2 (t, 2H), 1.5 (m, 4H), 1.3 (s, 6H). Anal. calcd. for $C_{15}H_{19}ClFNO_4$: C, 54.3; H, 5.77; N, 4.22. Found: C, 54.27; H, 5.91; N, 4.14.

Preparation of N-(3-chloro-5-fluorosalicyloyl)-8-aminocaprylic Acid (8). Mp 94.5–96°C; ^{1}H NMR (DMSO-d_6) δ 13.6 (s, 1H), 12.0 (s, 1H), 12.0 (s, 1H), 9.1 (t, 1H), 7.8 (q, 1H), 7.65 (q, 1H), 3.3 (q, 2H), 2.2 (t, 2H), 1.55 (m, 4H), 1.3 (S, 6H). Anal. calcd. for $C_{15}H_{19}ClFNO_4$: C, 54.3; H, 5.77; N, 4.22. Found: C, 54.36; H, 5.79; N, 4.17.

Preparation of N-(4-methoxysalicyloyl)-10-aminobutyric Acid (9). Mp 130–134°C; ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 12.1 (s, 1H), 8.6 (t, 1H), 7.78 (d, 1H), 6.4 (m, 2H), 3.7 (s, 3H), 3.3 (q, 2H), 2.28 (t, 2H), 1.76 (m, 2H). Anal. calcd. for $C_{12}H_{21}NO_5$: C, 56.92; H, 5.93; N, 5.53. Found: C, 56.76; H, 5.89; N, 5.03.

Preparation of N-(4-methoxysalicyloyl)-10-aminodecanoic Acid (10). Mp 105–108°C; ^{1}H NMR (DMSO-d_6) δ 13.2 (s, 1H), 12.05 (s, 1H), 8.65 (s, 1H), 7.7 (d, 1H), 6.44 (m, 2H), 3.78 (m, 2H), 3.2 (q, 2H), 2.2 (t, 2H), 1.5 (m, 5H), 1.25 (s, 9H). Anal. calcd. for $C_{18}H_{27}NO_5$: C, 64.09; H, 8.01; N, 4.22. Found: C, 64.00; H, 8.17; N, 4.12.

Preparation of Sodium N-(3,5-dichlorosalicyloyl)-11-aminoundecanoate (11). A 500-mL Erlenmeyer flask equipped with a magnetic stir bar was charged with 12.0 g (31.0 mmol) of N-(3,5-dichlorosalicyloyl)-11-aminoundecanoic acid (prepared using the procedure detailed previously) and 200 mL of ethanol. The mixture was heated until most of the solids dissolved, hot filtered, and treated with a solution of 1.26 g (32.0 mmol) of sodium hydroxide and 3.76 mL of water. The mixture was stirred for 1 h, during which a white solid formed. The reaction mixture was concentrated to half the volume and diluted with 300 mL of heptane. The white solid was isolated by filtration and dried in vacuo, giving a total of 11.98 g of sodium N-(3,5-dichlorosalicyloyl)-11-aminoundecanoate, mp 195–210°C; ^{1}H NMR (DMSO-d_6) δ 11.86 (t, 1H), 7.5 (d, 1H), 7.08 (d, 1H), 3.2 (q, 2H), 2.17 (t, 2H), 1.47 (m, 4H), 1.35 (s, 12H). Anal. calcd. for $C_{18}H_{24}Cl_2NNaO_4$: C, 52.39; H, 5.86; N, 3.40; Na, 5.58. Found: C, 52.46; H, 5.92; N, 3.16; Nay 5.37.

Preparation of N-(3,5-dichlorosalicyloyl)-10-amonodecanoic Acid (12). Mp 95–99°C; ^{1}H NMR (DMSO-d_6) δ 13.75 (s, 1H), 9.14 (t, 1H), 7.99 (d, 1H), 7.75 (d, 1H), 3.27 (m, 2H), 2.2 (t, 2H), 1.49 (m, 4H), 1.24 (s, 10H). Anal. calcd. for $C_{17}H_{23}Cl_2NO_4$: C, 54.25; H, 6.16; N, 3.72. Found: C, 53.97; H, 6.14; N, 3.47.

Preparation of N-(4-hydroxyphenylacetyl)-8-aminocaprylic Acid (15). Mp 113–115°C; ^{1}H NMR (DMSO-d_6) δ 12.0 (s, 1H), 9.25 (s, 1H), 7.9 (t, 1H), 7.05 (d, 2H), 6.65 (d, 2H), 3.35 (s, 1H), 3.2 (s, 2H), 3.0 (q, 2H), 2.18 (t, 2H), 1.47 (t, 2H), 1.36 (t, 2H), 1.23 (s, 4H). Anal. calcd. for $C_{16}H_{23}NO_4$: C, 65.53; H, 7.85; N, 4.79. Found: C, 65.03; H, 8.09; N, 4.81.

Preparation of N-(3-hydroxyphenylacetyl)-8-aminocaprylic Acid (16). Mp 85–88°C; ^{1}H NMR (DMSO-d_6) δ 12.0 (s, 1H), 9.35 (s, 1H), 7.95 (s, 1H), 7.05 (t, 1H), 6.6 (m, 2H), 3.27 (s, 2H), 3.0 (q, 2H), 2.5 (m, 2H), 2.18 (t, 2H), 1.47

(m, 2H), 1.37 (m, 2H), 1.23 (s, 6H). Anal. calcd. for $C_{16}H_{23}NO_4$: C, 65.53; H, 7.85; N, 4.79. Found: C, 65.13; H, 7.86; N, 4.67.

Preparation of Oligo(3,5-dichlorosalicylate). Acetic anhydride (7.10 mL, 7.69 g, 0.075 mol, 1.04 eq.), 3,5-dichlorosalicylic acid (15.00 g, 0.0725 mol, 1.00 eq.), and xylenes (250 mL) were added to a 250-mL, three-neck flask fitted with a magnetic stir bar, a thermometer, and a Dean–Stark trap with condenser. The flask was placed in a sand bath and heating of the cloudy white mixture began. The reaction mixture became a clear solution around 115°C. Most of the volatile organics (xylenes and acetic acid) were distilled into the Dean–Stark trap over 3 h (133–142°C); a total of 40 mL was distilled. The residue, a tan solid, was placed in a crystallizing dish and allowed to dry under vacuum. The 15.28 g of oligosalicylate produced was used without further purification.

Preparation of 3-[4-(3,5-dichlorosalicyloyl)aminophenyl] propionic acid (14). A mixture of 0386-24A (12.0 g, 0.0698 mol, 1.10 eq.), 3-(4-aminophenyl)propionic acid (9.42 g, 0.0571 mol, 1.0 eq.), and dioxane (150 mL) were added to a 500-mL round-bottom flask equipped with a magnetic stir bar and a condenser. A tan slurry formed. The reaction mixture was heated to reflux for approximately 5 h. The reaction was determined to be complete by HPLC. The clear brown reaction mixture was cooled to room temperature. The dioxane was removed in vacuo. The sticky solid residue was taken up in 2N NaOH (200 mL). The cloudy yellow-brown mixture was filtered and extracted with ethyl acetate (350 mL). The clear yellow-brown aqueous layer was acidified with 2N HCl. A tan solid precipitated and was recovered by filtration. The solid was taken up in ethanol/water (50:50), decolorized with activated carbon, and crystallized. A tan solid formed and was recovered by filtration drying under vacuum (50°C) overnight to yield 9.3 g (46%) of 3-[4-(3,5-dichlorosalicyloyl)aminophenyl)] propionic acid, mp 225°C; ^{1}H NMR (DMSO-d_6) δ 12.9 (s, 1H), 12.15 (sm 1H), 10.6 (s, 1H), 8.1 (d, 1H), 7.8 (d, 1H), 7.5 (d, 2H), 7.25 (d, 2H), 2.8 (t, 2H), 2.5 (m, 2H). Anal. calcd. for $C_{16}H_{13}Cl_2NO_4$: C, 54.24; H, 3.67; N, 3.95. Found: C, 54.21; H, 3.68; N, 3.89.

REFERENCES

1. Beckwith, A. L. J. Synthesis of amides. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley: New York, 1970; 73–185.
2. Larock, R. C. *Comprehensive Organic Transformation*, 2nd Ed.; VCH: New York, 1999; 1941–1994, 1953–1954, 1957–1958, 1973–1976.
3. For instance 4-nitrophenol is well used as a leaving group in peptide synthesis Bodanszky, M.; du Vigneaud, V. A method of synthesis of long peptide chains using a synthesis of oxytocin as an example. *J. Am. Chem. Soc.* **1959**, *81*, 5688–5691.
4. (a) Saegusa, T.; Tokuzawa, T.; Kobayashi, S. Polymerization of anhydro-o-carboxysalicylic acid. *Poly. Bull.* **1979**, *1*, 341–345; (b) White, D. M.; Socha, L. A. Method for preparing polysalicylates. US patent 4,855,483, August 8, 1989.