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PII: S0040-4039(19)30232-1
DOI: https://doi.org/10.1016/j.tetlet.2019.03.024
Reference: TETL 50665

To appear in: *Tetrahedron Letters*

Received Date: 15 January 2019
Revised Date: 1 March 2019
Accepted Date: 8 March 2019

Please cite this article as: Walker, D.P., Davis Harris, G. Jr, Carroll, J.N., Boehm, T.L., McReynolds, M.D., Struble, J.R., van Herpt, J., van Zwieten, D., Koeller, K.J., Bore, M., A new process to prepare 3,6-dichloro-2-hydroxybenzoic acid, the penultimate intermediate in the synthesis of herbicide dicamba, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.03.024

A new process to prepare 3,6-dichloro-2-hydroxybenzoic acid, the penultimate intermediate in the synthesis of herbicide dicamba

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Highlights

- 3,6-dichloro-2-hydroxybenzoic acid (3,6-DCSA) can be prepared in four steps from salicylic acid.
- 3,6-DCSA can be prepared without the need of an expensive high pressure, high temperature Kolbe-Schmitt carboxylation.
- 3,6-DCSA can be prepared in 60% overall yield and >98% purity commencing from salicylic acid.

Abstract

Glyphosate [N-(phosphonomethyl)glycine] is a broad spectrum, post-emergent herbicide that is among the most widely used agrochemicals globally. Over the past 30 years, there has been a development of glyphosate-resistant weeds, which pose a significant challenge to growers and crop scientists, resulting in lower crop yields and increased costs. 3,6-Dichloro-2-methoxybenzoic acid (dicamba) is the active ingredient in XtendiMax®, a standalone herbicide developed by Bayer Crop Science to control broadleaf weeds, including glyphosate-resistant species. 3,6-Dichloro-2-hydroxybenzoic acid (3,6-DCSA) is the penultimate intermediate in the synthesis of dicamba. Existing dicamba manufacturing routes utilize a high temperature, high pressure Kolbe-Schmitt carboxylation to prepare 3,6-DCSA. Described in this Letter is a new, non-Kolbe-Schmitt process to prepare 3,6-DCSA from salicylic acid in four chemical steps.

Keywords: salicylic acid, chlorination, hydrodebromination, dicamba

Introduction

Glyphosate [N-(phosphonomethyl)glycine] is a broad spectrum, post-emergent herbicide that was first registered in the U.S. in 1974. In addition to the development of glyphosate-tolerant crops, the superior efficacy, safety, and environmental profiles of glyphosate relative to other broad-spectrum herbicides led to an exponential increase in global adoption rates in agricultural and lawn & garden markets. Over the past 30 years, there has been a development of several glyphosate-resistant weeds, including ragweed, pigweed, horseweed and waterhemp.[1]. Weed resistance poses a significant challenge to growers and crop scientists, leading to lower crop yields and increased costs. Monsanto, which was acquired by Bayer AG in 2018, developed XtendiMax®, a standalone herbicide designed to help manage glyphosate-resistant weeds. The active ingredient in XtendiMax® is 3,6-dichloro-2-methoxybenzoic acid (dicamba), a broad-spectrum herbicide first registered in 1967.

Dicamba is currently manufactured by two different synthetic routes, the Trichlorobenzene (TCB) Process [2] and the Dichlorobenzene (DCB) Process (Scheme 1). Both processes utilize 2,5-dichlorophenol (2,5-DCP) as a common intermediate. In the TCB Process, 1,2,4-trichlorobenzene is hydroxylated to afford a mixture of 2,5-DCP, 2,4-DCP and 3,4-DCP in a 62:16:22 ratio, respectively [2,3,4] Fractional distillation of the phenolic mixture removes the 3,4-DCP isomer and a fractional crystallization removes the 2,4-DCP isomer to afford a 46% yield of 2,5-DCP with a purity of 98%. [4] In the DCB Process, 2,5-DCP is prepared in four synthetic steps from 1,4-dichlorobenzene (1,4-DCB) via nitration, [5] catalytic hydrogenation, [6]diazotization of 2,5-dichloroaniline (2,5-DCA) and subsequent hydrolysis. [7]A high pressure, high temperature Kolbe-Schmitt carboxylation of 2,5-DCP gives rise to 3,6-dichloro-2-hydroxybenzoic acid (3,6-DCSA) in 42% yield. Methylation using either methyl chloride [8] or dimethyl sulfate[Error! Bookmark not defined.] affords dicamba.

The TCB Process produces dicamba in 18% overall yield using three synthetic steps, whereas the DCB Process produces dicamba in higher overall yield (32%) but requires six synthetic steps. [9]Both processes utilize inexpensive reagents and can be used to generate large volumes of dicamba. However, there are significant challenges associated with each process. Step 1 of the TCB Process produces

a mixture of three dichlorinated phenols that is difficult to separate, requiring a distillation and crystallization to produce pure 2,5-DCP. While the DCB Process selectively produces 2,5-DCP as a single isomer, it requires four chemical steps. Moreover, both processes involve a capital intensive high temperature, high pressure carboxylation of 2,5-DCP. The yield of the carboxylation is low, requiring separation and recycling of unreacted 2,5-DCP. For both processes, the above issues contribute significantly to the overall manufacturing cost of dicamba. The commercial success of any agricultural product highly depends on achieving a low cost of goods. In the work described herein, we detail our efforts to develop a proprietary, commercially viable process to prepare dicamba.

Results and Discussion

Despite decades of research on new synthetic approaches to dicamba, manufacturing still relies on one of the two processes described above. The synthetic challenge with dicamba is to selectively arrange the substituents on the benzene ring in a 1,2,3,4-tetrasubstituted pattern. While searching for a new process to prepare dicamba, we came across a report by Hanna [10] who showed that chlorination of 3,5-dichlorosalicylic acid in oleum gave a 93% yield of 3,5,6-trichlorosalicylic acid (3,5,6-TCSA) with no mention of other isomers (Scheme 2). This reaction was of interest to us because the substitution pattern of two of the three chlorine atoms was the same substitution pattern found in dicamba. Taken a step further, we envisioned a synthetic route to prepare dicamba from salicylic acid (SA) (Scheme 3). SA was an ideal starting material for the preparation of dicamba as it is inexpensive [11]and readily available in high purity and large quantity. SA also contains the key carboxylic acid moiety found in dicamba; hence, the high temperature, high pressure carboxylation needed in the existing manufacturing routes would be avoided. To circumvent chlorination in the 5-position, a bromine atom would serve as a blocking group to force chlorination into the 3- and 6-positions of SA. Literature has shown that 5-bromo-salicyclic acid can be prepared from SA. [12] Chlorination of 5-BSA would give 5-bromo-3,6-dichlorosalicylic acid (BDCSA). Selective hydrogenolysis of the bromine atom would afford 3,6-DCSA. For the chlorination step, a quick check of the literature showed that halogenation in oleum can be safely carried out on large scale. [13] For the hydrodebromination step, literature suggested that an aryl bromide could be selectively removed in the presence of an aryl chloride using catalytic hydrogenolysis. [14]

Armed with these earlier studies, our first task in developing a new dicamba process was to establish that dicamba could be prepared selectively from 5-BSA in a proof-of-concept study. Toward this end, treatment of 5-BSA with chlorine [15] in 20% oleum, followed by drowning the reaction mixture in ice water gave a 69% yield of BDCSA (Scheme 4). Surprisingly, BDCSA had yet to be described in the literature prior to this work. Hydrogenolysis of BDCSA selectively removed the bromine atom, giving rise (85%) to 3,6-DCSA. Methylation of 3,6-DCSA using the literature procedure[Error! Bookmark not defined.] afforded dicamba that was consistent in all respects to an authentic sample of dicamba.

Having achieved a proof-of-concept, we next performed optimization studies to streamline the process and lower the cost of goods. While 5-BSA is commercially available, it is technical grade material containing up to 12% other isomers. Thus, we back-integrated our process to salicylic acid. Furthermore, since the industrial process to convert 3,6-DCSA into dicamba is well established and efficient and our process utilized this key intermediate, we focused our efforts on developing a commercially viable process to convert SA into 3,6-DCSA. Shown below are process optimization studies for each of those steps. [16]

Bromination of SA:

Literature has shown that 5-BSA can be prepared by treating SA with bromine in acetic acid with[**Error! Bookmark not defined.**a] or without[**Error! Bookmark not defined.**b] added sulfuric acid. In our hands, bromination of SA in acetic acid gave an 85% yield of 5-BSA, together with a significant amount of 3-BSA (Table 1, Entry 1). Hewitt found that the amount of the 3-isomer could be reduced by adding 2.0 equivalents of concentrated sulfuric acid.[**Error! Bookmark not defined.**a] We confirmed Hewitt's results (Entry 2); unfortunately, a substantial amount of 3,5-DBSA was also formed. Interestingly, the total amount of bromine incorporated into the product mixture (1.3 equiv.) was higher than the 1.1 equivalents of bromine charged to the rector. As it is known that sulfuric acid can oxidize bromide ion to bromine, [17] we suspected that the extra bromine incorporation was due to additional bromine being generated throughout the reaction. Taking advantage of this observation, we lowered the bromine charge to 0.65 equivalents (Entry 3). While the amount of 3,5-DBSA was substantially reduced, an unacceptable amount of 3-BSA still formed. Up to that point, all reactions had been conducted in acetic acid solvent. Realizing that acetic acid had to be removed prior to the chlorination in oleum, we were pleased to observe that the bromination of SA could be conducted in neat sulfuric acid (Entries 4-6). Our optimized conditions gave a 96% yield of 5-BSA using only 0.55 equivalents of bromine (Entry 6). Furthermore, only small amounts of 3-BSA and 3,5-DBSA were produced.

Chlorination of 5-BSA:

In our proof-of-concept study, 5-BSA was directly converted to BDCSA using chlorine in 20% oleum. However, these conditions produced 15-20% sulfonylated byproduct **1**. To minimize the formation of **1**, a step-wise chlorination was pursued. Toward this end, the crude solution of 5-BSA in 96% sulfuric acid (2.3 M) was directly treated with chlorine gas at 35-40 ˚C to form 5-bromo-3-chlorosalicylic acid (BCSA) (Table 2, Entry 1). However, the chlorination usually took greater than ten hours to complete due to precipitation of BCSA that increased throughout the reaction, making stirring difficult. Running the reaction at higher temperatures produced significant amounts of **1**. Initially, the issue was resolved by diluting the sulfuric acid solution of 5-BSA from 2.3 M to 1.3 M with additional concentrated sulfuric acid (Entry 2). This allowed better stirring throughout the chlorination as more product (BCSA) remained in solution. The chlorination also went to completion in 8 h. Alternatively, it was found that the BCSA was significantly more soluble in 2% oleum than 96% sulfuric acid. Taking advantage of this, the 2.3 M sulfuric acid solution of 5-BSA was fortified to the 2% oleum level by blending it with commercial 65% oleum. Under these conditions, the chlorination reaction was complete in ca. 8 h (Entry 4). Fortunately, the amount of sulfonylated byproduct **1** was similar to those levels seen using 96% sulfuric acid (1.3 M).

A second challenge that arose during the chlorination of 5-BSA was the amount of 3,5-DBSA would rise significantly once the chlorination began (typically from 2% to 8-10%). We realized this was due to unreacted bromine still present at the end of the bromination. This issue was minimized by placing the crude 5-BSA mixture under vacuum (25-30 mm Hg) for one hour prior to chlorination. This operation lowered the amount of 3,5-DBSA from 8-10% to 2-3% (Table 2, Entries 3 and 4).

Chlorination of BCSA:

The crude solution of BCSA in 2% oleum was cooled to 10 ˚C and fortified to the 20% oleum level by blending it with 65% oleum. Iodine (1.0 mol%) was added, and the mixture was chlorinated at 35 ˚C. The chlorination was typically complete in four hours. Without added iodine, the yield of BDCSA was only 20-25%. Presumably, iodine monochloride is generated in the reaction. To test this, we replaced iodine with 1 mol% iodine monochloride, and identical results were produced. However, without further experimentation, the active chlorinating species in the reaction is not known.

As part of a cost savings measure, we attempted to minimize sulfuric acid usage in our process. Toward this end, we evaluated running the chlorination reaction at higher concentrations (Table 3). However, as the concentration of BCSA in 20% oleum increased, impurities, such as 3,5,6-TCSA, also increased (Entry 2). Once a BCSA concentration of 1.3M was reached, no BDCSA formed (Entry 3). Interestingly, Hanna[**Error! Bookmark not defined.**b] and others [18] have stressed the importance of maintaining a minimum of four mols of free sulfur trioxide per mol of substrate to avoid impurity formation. In the case of Entry 3, the molar ratio of sulfur trioxide to BCSA fell below four. Interestingly, if the 1.3 M BCSA reaction was fortified to 25% oleum, a sulfur trioxide-to-BCSA molar ratio of 5.3 was obtained, and this change restored BDCSA and impurity levels to those seen at lower BCSA concentrations (Entry 4).

Once the chlorination was complete, it was drowned in ice water and solid BDCSA was subsequently isolated as a solid. Table 4, Entry 1 shows the product (BDCSA) and impurity profile for the isolated solid. The structure of self-condensed ester **2** was confirmed by ^{1}H NMR spectroscopy and high-resolution mass spectrometry, and it formed during the ice water quench as it was not detected prior to workup. Compound **3** was an impurity formed via chlorination of 3,5-DBSA. While the ice water quench worked satisfactorily in the lab, it did not represent an operation that could be easily carried out on large scale. Also, our long-term goal was to recycle sulfuric acid utilized in the process. The ice water quench generated dilute sulfuric acid, which was not suitable for recycle. Hence, the workup needed to be modified.

Our optimized workup involved diluting the 25% oleum solution with 75% aqueous sulfuric acid to generate 96% sulfuric acid. Towards the end of the dilution, the product (BDCSA) precipitates. After filtering and washing, the BDCSA wet cake was ready for the hydrodebromination. Fortunately, self-condensed ester byproduct **2** was less than one percent using the 75% sulfuric acid quench, which improved the overall yield of BDCSA (Table 4, Entry 2). Also, the amount of heat generated during the 75% sulfuric acid quench was significantly less than the ice water quench. The 96% sulfuric acid mother liquor was reused to make new batches of BDCSA of similar purity to those using fresh sulfuric acid (Entry 3).

Hydrodebromination of BDCSA:

The preferred catalyst for the hydrodebromination was palladium on activated carbon. [19] Other catalysts surveyed, such as palladium hydroxide, Raney Nickel or platinum on carbon were not effective. During the proof-of-concept studies, the hydrodebromination was conducted in acetic acid using sodium acetate to neutralize the liberated hydrobromic acid. While these conditions converted BDCSA into 3,6-DCSA in good yield and ca. 95% selectivity, integrating those conditions with the final methylation step to form dicamba was going to be challenging. Also, to conserve cost, our long-term plan for the hydrodebromination involved recycling the liberated bromide ion back to bromine for use in the bromination step. Bromine manufacturers prefer aqueous bromide feed streams containing minimal organic impurities. [20] This raised a second challenge with using acetic acid in the hydrodebromination: it was going to be difficult to efficiently isolate sodium bromide as an aqueous stream free of acetic acid. Thus, we needed to identify an alternate solvent system for the hydrodebromination reaction.

The optimized conditions for the hydrodebromination involved an ethyl acetate-water mixture wherein aqueous sodium hydroxide was added in portions to neutralize the liberated hydrobromic acid. Once the reaction was complete and the catalyst was removed, what remained was a biphasic mixture consisting of an organic layer containing 3,6-DCSA and an aqueous sodium bromide layer. Table 5

shows product and impurity levels for the hydrodebromination under different reaction conditions. The main byproducts were 3-chlorosalicylic acid (3-CSA), 6-chlorosalicylic acid (6-CSA) and 3,5,6-TCSA.

The final stage of the process involved isolation and purification of 3,6-DCSA. Toward this end, a solvent swap from ethyl acetate to xylenes was carried out. Once the ethyl acetate had been removed, the mixture was slurried in hot xylenes. Isolation and drying of the product afforded 3,6-DCSA in 98.1% purity (77% mass recovery, Table 5). The byproducts identified in 3,6-DCSA were 3-CSA (1.4%) and 6-CSA (0.3%) and 3,5,6-TCSA (0.2%). All other byproducts were present in less than 0.1%.

A summary of our synthesis of 3,6-DCSA from SA that includes the above process improvements is shown in Scheme 5. The process produced 3,6-DCSA in 60% overall yield from SA and in 98% purity. [21]

In summary, we have developed a new process for preparing 3,6-DCSA, the penultimate intermediate in the synthesis of dicamba. The new route commences from SA, an inexpensive and readily available raw material. Our approach utilizes a telescoped process for converting SA into novel compound BDCSA, which minimizes solvent usage and unit operations. The final step features a selective conversion of BDCSA into 3,6-DCSA. The process converts SA into 3,6-DCSA in four chemical steps, which is two steps more than the TCB Process but one step less than the DCB Process. The new route avoids the capital-intensive Kolbe-Schmitt carboxylation used in the current manufacturing processes. Furthermore, the sequence produces 3,6-DCSA in 60% overall yield and 98% purity, which is competitive with the existing dicamba manufacturing routes.

Acknowledgment

We thank Doug Malkin, Karen Regina and Wensheng Li for analytical support. We thank Dan Dukesherer for a generous supply of 3,6-DCSA and dicamba. We thank Bayer Crop Science St. Louis Chemistry Leadership for encouraging the publication of this work.

References

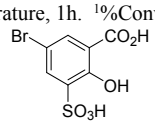
[1] For a full list of glyphosate-resistant weeds, see: http://weedscience.org/Summary/ResistbyActive.aspx
[2] Richter, S. B. US Patent 3,013054, December 12, 1961.
[3] Widiger, A. H.; Aaron, M. L.; Dugan, G. F. US Patent 2,799,714, July, 16th, 1957.
[4] Payne, K. R.; Milnes, M. H. US Patent 3,726,929, April 10th, 1973.
[5] Csikos, R. US Patent 4,207,261, June 10th, 1980.
[6] Greenfield, H.; Dovell, F. S. *J. Org. Chem.* **1967,** *32*, 3670.
[7](a) Wataya, M.; Onodera, N.; Imamura, S. US Patent 4,005,151, June 25th, 1977; (b) De Kort, B.; McReynolds, M. D.; Parlow, J. J.; Woerndle, R. S. US Patent 9,695,114, July 4th, 2017.
[8] Kim, D.-W. US Patent 4,161,611, July 17th, 1979.
[9] Dicamba manufacturing typically recovers and recycles 2,5-DCP. Assuming recovery and recycling of 2,5-DCP improves the yield of 3,6-DCSA to 90%, then the overall yield of dicamba for the TCB and DCB Processes improves to 39% and 68%, respectively.
[10] (a) Hanna, D. L. US Patent 3,062,877, November 6th, 1962; (b) Farinholt, L. H.; Stuart, A. P.; Twiss, D. *J. Am. Chem. Soc.* **1940,** *62*, 1237.
[11]Industrial grade salicylic acid is more expensive than 1,4-dichlorobenzene but less expensive than 1,2,4-trichlorobenzene.
[12] (a) Hewitt, J. T.; Kenner, J.; Silk, H. *J. Chem. Soc., Trans.* **1904**, *85*, 1225-1230; (b) Hirwe, N. W.; Patil, B. V. *Proc. Indian Acad. Sci., Sec. A* **1937,** 321.
[13] For the large scale use of oleum as a solvent, see: (a) Khuddus, M. A. US Patent 5,049,601, September 17th, 1991; (b) Gelmont, M.; Oren, J. *Org. Process Res. Dev.* **2002,** *6*, 591; (c) Dale, D. J.; Draper, J.; Dunn, P. J. ; Hughes, M. L. ; Hussain, F. ; Levett, P. C.; Ward, G. B.; Wood, A. S. *Org. Process Res. Dev.* **2002,** *6*, 767.
[14] *Cf:* Becher, H. M.; Sehring, R. US Patent 3,928,432, December 23rd, 1975.
[15] On a laboratory scale, we demonstrated that using 0.68 equivalents (2.05 eq. of active chlorine) of 2,4,6-trichloroisocyanuric acid (ACL 90) gave very similar yields of BDCSA to that of chlorine gas.
[16] Boehm, T. L.; Bore, M.; Carroll, J. N.; Harris, Jr., G. D.; McReynolds, M. D.; Struble, J. R.; Walker, D. P. US Patent 9,856,201, January 2nd, 2018.
[17] Proskouriakoff, K. *J. Phys. Chem.* **1929,** *33*, 717.
[18] Manfre, R. J.; Mohan, A. G.; Rauhut, M. M. US Patent 4,308,395, December 29th, 1981.
[19] In a few instances, the hydrodebromination using palladium on activated carbon would fail to produce 3,6-DCSA. It was determined that iodine from the prior chlorination was not completely washed away from BDCSA wet cake and subsequently poisoned the palladium catalyst. However, reslurrying BDCSA wet cake in xylenes at 80 °C for 4 h removed the catalyst poison and hydrodebromination was restored.
[20] Davis, W. T. US Patent 3,181,934, May 4th, 1965.
[21] If a purity greater than 99% for 3,6-DCSA is desired, it can be reslurried in dichloromethane (3 mL/g) to afford 3,6-DCSA [99.3% purity (HPLC and ^{1}H NMR), 97% mass recovery].

Scheme 1. Industrial syntheses of dicamba. *Reagents and conditions, TCB Process*: (a) KOH, MeOH, poly ethylene glycol, 32 atm., 180 ˚C, 7h; (b) fractional distillation; (c) fractional crystallization; (d) aq. KOH, xylene, azeotropic drying; CO_2, 500 psi, 135 ˚C, 8 h; (e) aq. NaOH, CH_3Cl, 90 psi, 85 ˚C, 10 h; (f) aq. KOH, dimethyl sulfate, 100 ˚C, 3h; *DCB Process:* (g) HNO_3, H_2SO_4; (h) H_2, Pt/C, HOAc, (60 psi); (i) $NaNO_2$, aq. H_2SO_4; (j) steam distillation.
Scheme 2. Hanna's preparation of 3,5,6-TCSA.
Scheme 3. Synthetic plan to prepare dicamba from salicylic acid.

Scheme 4. Preparation of dicamba from 5-BSA. *Reagents and conditions:* (a) Cl_2, 20% oleum, 40 ˚C, 3 h; (b) H_2 (1 atm.), 5% Pd/C, NaOAc, HOAc, room temperature, 2 h; (c) CH_3Cl, aq. NaOH, 90 psi, 85 ˚C, 10 h.

Scheme 5. Optimized process for converting SA into 3,6-DCSA. *Reagents and conditions:* (a) Br_2 (0.55 equiv.), 96% H_2SO_4, 5 ˚C → room temperature, 2 h; (b) 2% oleum (fortified with 65% oleum), 10 ˚C; Cl_2, 35-40 ˚C, 7 h; (c) 25% oleum (fortified with 65% oleum), 10 ˚C; Cl_2, 35 ˚C, 3 h; (d) dilute with 75% H_2SO_4, 5 ˚C, filter precipitate, wash with 75% H_2SO_4 and water; (e) H_2 (1 atm.), 5% Pd/C, 2.5M aq. NaOH, EtOAc-H_2O (4:1), room temperature, 4 h; (f) Remove aqueous layer, solvent swap EtOAc → xylenes; slurry 80 ˚C, 4 h; (g) filter precipitate, room temperature, dry in vacuo.

Table 1. Bromination of SA: Effect of bromine equivalents and sulfuric acid on product distribution. *Reagents and conditions:* (A) AcOH (1.0 M), 30-60 ˚C, 2 h; (B) AcOH (1.0 M), 96% H_2SO_4 (2.0 equiv.), 30-60 ˚C, 2 h; (C) 96% H_2SO_4 (1.0 M), 5 ˚C → room temperature, 1h; (D) 96% H_2SO_4 (2.3 M), 5 ˚C → room temperature, 1h. [1]%Conversion = (100 – HPLC area% of SA). [2]Numbers indicate HPLC area % except for Entry 6, which was also determined by ^{1}H NMR (600 MHz).



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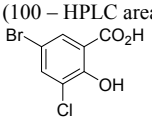
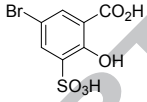


BCSA

Entry	Br_2 (eq)	Condi-tions	%Conv-ersion[1]	Product Ratio[2] [5-BSA : 3-BSA : 3,5-DBSA]
1	1.1	A	97	85 : 7 : 3
2	1.1	B	>99	80 : 2 : 18
3	0.65	B	>99	90 : 6.5 : 3.1
4	1.0	C	>99	91 : <1 : 9
5	0.50	C	80	96 : 3 : 1
6	0.55	D	>99	96 : 1.4 : 2.6

Table 2. Chlorination of 5-BSA: *Conditions:* (A) Cl_2, 2.3 M 5-BSA in 96% H_2SO_4, no vacuum applied prior to chlorination, 55 ˚C, 16 h; (B) Cl_2, 1.3 M 5-BSA in 96% H_2SO_4, no vacuum applied prior to chlorination, 40 ˚C, 7 h; (C) Cl_2, 1.3 M 5-BSA in 96% H_2SO_4, 25-30 mm Hg vacuum applied for 1 h prior to chlorination, 40 ˚C, 7 h; (D) Cl_2, 2.3 M 5-BSA in 2% oleum, vacuum applied prior to chlorination, 55 ˚C, 8 h. [1]%Conversion = (100 – HPLC area% of 5-BSA). [2]Numbers indicate HPLC area %.



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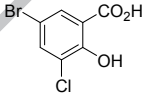


BCSA

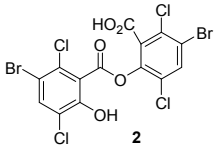
Entry	Chlorination Conditions	%Conv-ersion[1]	Product Ratio[2] [BCSA : 3,5-DBSA : **1**]
1	A	48	32 : 8 : 8
2	B	98	83 : 11 : 4
3	C	98	91 : 3 : 4
4	D	99	90 : 3 : 6

Table 3. Effect of BCSA concentration and oleum strength on impurity formation. [1]%Conversion of BCSA to products in all entries was ~98. [2]Numbers indicate HPLC area %. [3]Other byproducts (see: Table 4 for full list, *vide infra*) were also affected by the SO_3:BCSA molar ratio; however, only 3,5,6-TCSA is shown to illustrate the effect.

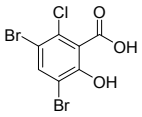
Entry	[BCSA] (M)	% Oleum	Molar Ratio (SO_3:BCSA)	% BDCSA[1,2]	% 3,5,6-TCSA[2,3]
1	0.46	20	10	89	2.4
2	0.92	20	5.2	83	4.2
3	1.3	20	3.8	<1	>10
4	1.3	25	5.3	84	5.1

Table 4. (A) Drown reaction mixture in ice water; extract product into EtOAc; (B) Dilute reaction with 75% H_2SO_4; filter precipitate; partition between EtOAc and water. [1]%Conversion = (100 – HPLC area% of BCSA) [2]Numbers indicate HPLC area% of the EtOAc layer. [3]Approximately 5wt% of sulfonic acid **1** was

also present; however, this byproduct was lost to the aqueous layer during workup. [4]BDCSA prepared from SA using recycled 96% H_2SO_4.



2



3

Entry	Workup Conditions	%Conv-ersion[1]	Product Ratio[2,3] [BDCSA : **1** : **2** : **3** : 3,5,6-TCSA]
1	A	97	77 : 4 : 4 : 10 : 3
2	B	97	84 : 4 : <1 : 7 : 4
3	B[4]	97	85 : 1 : <1 : 6 : 6

Table 5. Hydrodebromination of BDCSA: Product and impurity profiles. (A) NaOAc, HOAc; (B) 2.5 M aq. NaOH (0.95 equiv.), EtOAc-water (4:1); (C) xylenes reslurry of crude 3,6-DCSA, 80 °C, 4 h. [1]All reactions were run at ambient temperature using 5% palladium on activated carbon (50% water content, 1.5 mol%) under 1 atmosphere of hydrogen. [2]%Conversion = (100 – HPLC area% of BDCSA). [3]Numbers determined by HPLC area% except Condition C, which was also determined by ^{1}H NMR (600 MHz).

Conditions[1]	%Conv-ersion[2]	Product Ratio[3] [3,6-DCSA : 3-CSA : 6-CSA : 3,5,6-TCSA]
A	>99	80 : 7 : 7 : 6
B	>99	78 : 9 : 7 : 6
C	-	98.1 : 1.4 : <0.1 : 0.2