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Technical Notes

Purification of 2,4 Dichlorobenzoic Acid

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Abstract:

A practical and efficient method to purify 2,4-dichlorobenzoic acid is described. The formation of an α-methylbenzylamine salt reduces the levels of positional isomer impurities to <0.05%. Although this purification method is not universal for all substituted benzoic acids, it was shown to be applicable to several other benzoic acids.

Introduction

One of the basic goals of process development is to understand the impurity profile of the drug substance, including the origin of the impurities, and then demonstrate their control throughout the process. The ICH guidelines[1] for impurities are described in Table 1. These values have been established to limit exposure of unqualified impurities to <1 mg/day.

The lower limits, applicable for a high dose compound, necessitate a very tight control of both the starting materials and the process. Aromatic, positional isomers are often especially challenging to control to very low levels. Although some impurities may be rejected during chemical processing, it is often more prudent to limit their introduction in the starting material. This is especially true if the synthesis is short and/or the starting material is introduced late in the synthetic route. During the development of a drug candidate we have addressed the need for isomerically pure 2,4-dichlorobenzoic acid (DCBA). Because DCBA is a commodity chemical, there is no shortage of suppliers worldwide and the pricing is competitive. Unfortunately, the major market for DCBA is not pharmaceutical and most vendors do not test for or control the levels of positional isomers. DCBA is used extensively in the polymer industry as a chain modifier for polyamides and organosilicone polymers; it is also further functionalized in other products as depicted in Figure 1.

Thorough testing of multiple lots of DCBA from the multiple vendors revealed significant variation in which isomers were present, and their levels were as seen in Table 2.

Table 1. **ICH guidelines for impurities in new drug substances**

maximum daily dose[a]	reporting threshold[b,c]	identification threshold[c]	qualification threshold[c]
≤2 g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day (whichever is lower)
>2 g/day	0.03%	0.05%	0.05%

[a] The amount of drug substance administered per day. [b] Higher reporting thresholds should be scientifically justified. [c] Lower thresholds can be appropriate if the impurity is unusually toxic.

The likely synthetic route for DCBA is outlined in Scheme 1.[2,3] The positional isomer impurities are formed during the dichlorination of toluene. The purity can be controlled at this stage by fraction distillation or zeolite adsoption.[4] However, it is unclear if the existing technology can achieve the desired level of purity, which is no impurity >0.05%. Furthermore, the globalization of commodity chemicals makes it unlikely that the same sources of raw materials will be used or even available for future material needs.

Since the quantity of DCBA needed for the pharmaceutical market is low, we had minimal success influencing vendors to produce material of exceptionally high quality. Qualification of the potential impurities is an option, but we prefer to develop a control strategy that limits the introduction of impurities and minimizes patient exposure. To this end we sought to develop a process that could purify commercial grade DCBA of all positional isomers to <0.05%. Not surprisingly, a screen of potential recrystallization solvents did not offer any purification.

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(1) Impurities in New Drug Substances Q3A(R2): 2006, ICH Harmonized Tripartite Guideline.

(2) These are a few patents describing the chlorination of toluene: Dewkar, G. K.; Thakur, V. Vi.; Pardhy, S. A.; Sudalai, A.; Devotta, S. Catalytic process for regiospecific chlorination of alkanes, alkenes and arenes. U.S. Patent 6,825,383, 2004. Catalytic production of 2,4-dichlorotoluene. Gelfand, S. U.S. Patent 4,006,195, 1977. DiBella, E. P. Production of 2,4-dichlorotoluene. U.S. Patent 3,366,698, 1968.

(3) (a) Nomura, K.; Myawaki, T. Preparation of aromatic carboxylic acids by using palladium-phosphine-type catalysts. JP 08104661 A 19960423, 1996; *Chem. Abstr.* 1996, *125*, 86311. (b) Kajisori, S.; Kakinami, T. Preparation of benzoic acid derivatives. JP 02268123 A 19901101, 1990; *Chem. Abstr.* 1990, *114*, 163745.

(4) (a) Iwayama, K.; Yamakawa, S.; Kitano, Y.; Kitagawa, S. Method for separation of dichlorotoluene isomer mixture. JP 2000247913 A 20000912, 2000; *Chem. Abstr* 2000, *133*, 239705. (b) Carra, S.; Paludetto, R.; Storti, G.; Morbidelli, M.; Gurtner, B.; Commandeur, R. Separation of dichlorotoluene isomers by zeolites. Ger. Offen. DE 3637727. 1987; Chem. Abstr. 1987, *107*, 77415

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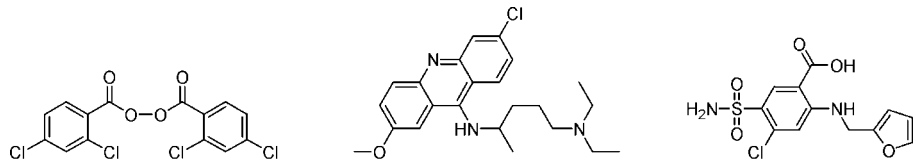


Figure 1. **Use of DCBA in commercial products.**

Table 2. **Vendor/isomeric impurity comparisons of DCBA**

			chlorobenzoic acid[a]		dichlorobenzoic acid[b]				
vendor	lot	year	2	4	2,5	2,6	3,4	all other	total impurities
I	A	2002			0.07		2.02		2.09
I	C	2002				0.03	0.06		0.09
I	D	2002			0.08	0.01	2.10		2.19
I	E	2002					0.04		0.04
I	F	2002					0.03		0.03
I	G	2005		0.08			0.06	0.06	0.20
I	H	2006	0.01	0.07		0.02	0.06	0.10	0.26
II		2006	0.52	0.13	0.07			0.30	1.02
III		2006						0.06	0.06
IV		2006		0.1			0.05	0.07	0.22
V		2006		0.02				0.03	0.05

[a] 3-Chlorobenzoic acid was not present in any samples. [b] 2,3-Dichlorobenzoic acid and 3,5-dichlorobenzoic acid were not present in any samples.

Scheme 1. **A commercial synthesis of DCBA**

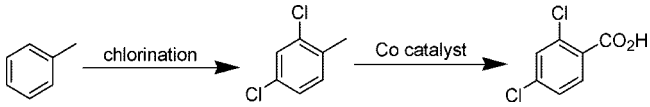


Table 3. **Salt screen of DCBA**

crystalline salt	reduction in isomers
sodium	none
potassium	none
ammonium	marginal
ethylenediamine	most <0.05
l-phenyl piperazine	most <0.05
(±)-α-methylbenzylamine	all <0.05
(*S*)-α-methylbenzylamine	all <0.05
tert-butylbenzylamine	all <0.05

A salt screen of common bases identified several crystalline salts.[5] As seen in Table 3, only a few salts provided purification.

Because the metal salts did not offer purification, it was desirable to have a counterion with a chromophore. This will simplify its detection and control in the reprocessed material. DSC analysis of the potential salts, Figure 2, indicated that the α-methylbenzylamine salt(s) should be the most stable and would potentially provide the highest level of purification.[6] Because our initial studies showed no advantage in using the enantiomerically pure amine, the racemate was preferred for price.[7]

A series of experiments were designed to test the rejection efficiency of the salt for all potential isomers. A solution of DCBA in isopropanol was spiked with positional isomers to an approximate level of 0.1%, 0.2%, 0.5%, 0.75%, and 1.0% of each isomer present in the solution. The mixture was heated to ensure complete dissolution, and 0.9 equiv of (±) α-methylbenzylamine was added at once. Upon cooling to room temperature the salt crystallized and formed a thick slurry. As depicted in Figure 3 below, there was significant purification across the board, and in most cases the desired limit of <0.05 was met during the initial salt formation.

The salts were isolated and dried to obtain yield information that was consistently ~70% when corrected for purity. Conditions were not optimized for this screen, and the yield is likely to improve with optimization. Reforming the free acid with HCl in methanol/water provided DCBA in ~80% yield. Additional purification was achieved during this step, and the resulting levels are represented in Figure 4 below.

As demonstrated above, both reprocessing steps afford purification, and this method can be used to reprocess material with up to 0.5% of all isomers present. Of course the commercial supplies do not have all isomers present. As seen in Table 2, there are usually only a couple present at ~0.1–0.2%, and they vary from lot to lot. The purification outlined in Scheme 2 was demonstrated on commercial bulk material and shown to be effective as demonstrated in the chromatogram (Figure 5).

We were interested to see if this purification was specific for the 2,4 isomer or generally applicable to other chlorobenzoic acids as well. Because all of the isomers are readily available, we tested all possible combinations (dichloro 2,6; 2,3; 2,5; 3,4; 3,5; as well as the monosubstituted 2; 3; 4). A series of spiking experiments at 0.2–0.3% were carried out for each of the above isomers. Whereas the process rejected all isomers to less than

(5) (a) Brzyska, W.; Swita, E. *Pol. J. Chem.* **1993**, *67*, 609. (b) Duff, J. G.; Yung, D. K.; Brenner, R. J.; Wilson, B. J.; Racz, W. J. *J. Chem. Educ.* **1969**, *46*, 388. (c) Levitin, E. Y.; Oridoroga, V. O. *Pharm. Chem. J.* **2003**, *37*, 653.

(6) Lattice energy is a good but not absolute correlation to impurity rejection.

(7) The precise nature of the salt, as a racemate or conglomerate, is unknown.

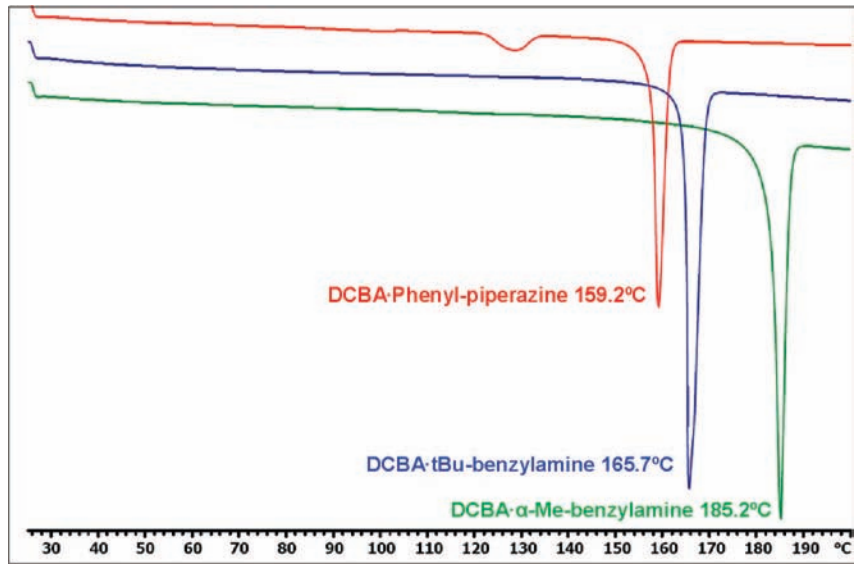


Figure 2. **DSC comparison of DCBA amine salts.**

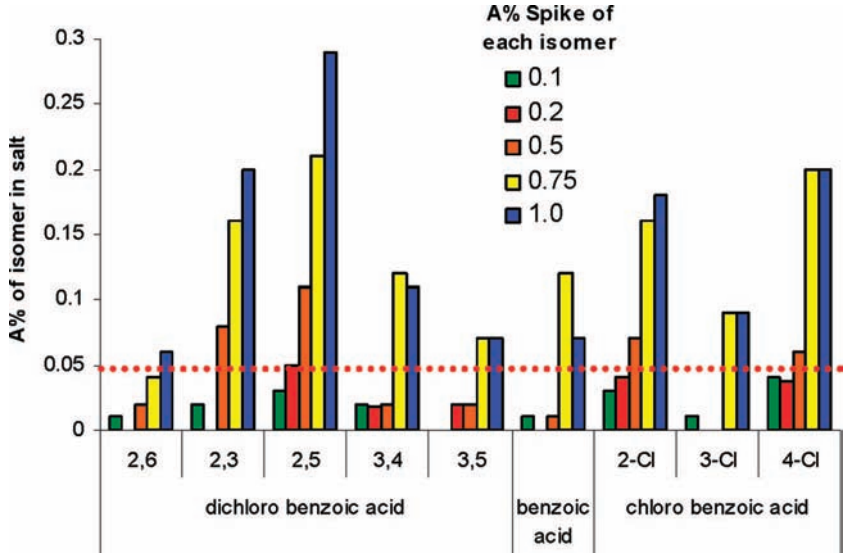


Figure 3. **Isomer rejection during α-methylbenzylamine·DCBA salt formation.**

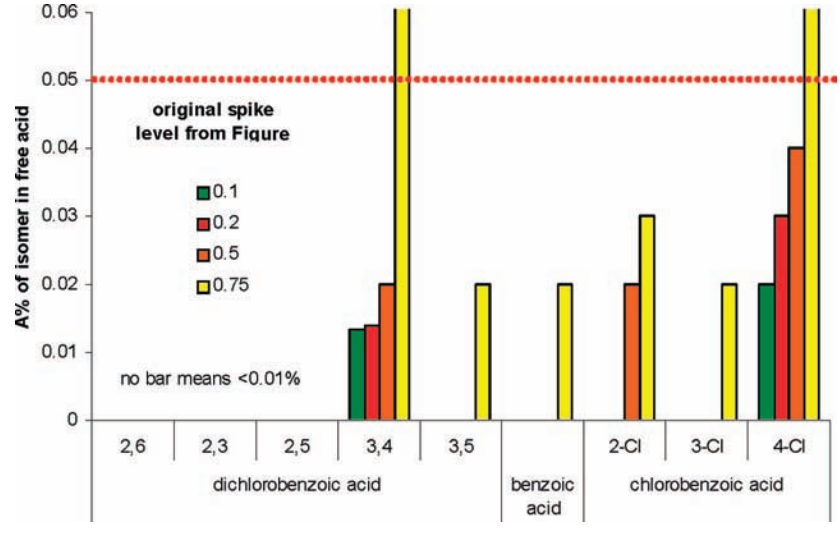


Figure 4. **Isomer rejection during breaking of α-methylbenzylamine·DCBA salt.**

0.05% for the 2,5 isomer, all of the others had at least one impurity that remained ≥0.05% as depicted in Figure 6 below.[8] This procedure may still be useful to purify other chloro isomers depending on the nature of the impurities present.

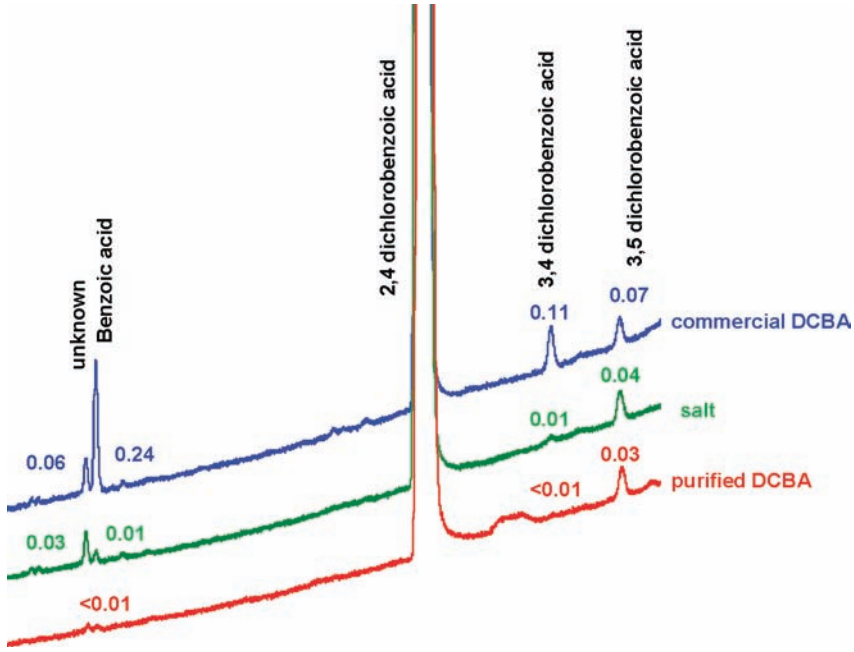


Figure 5. **HPLC overlay of purification process.**

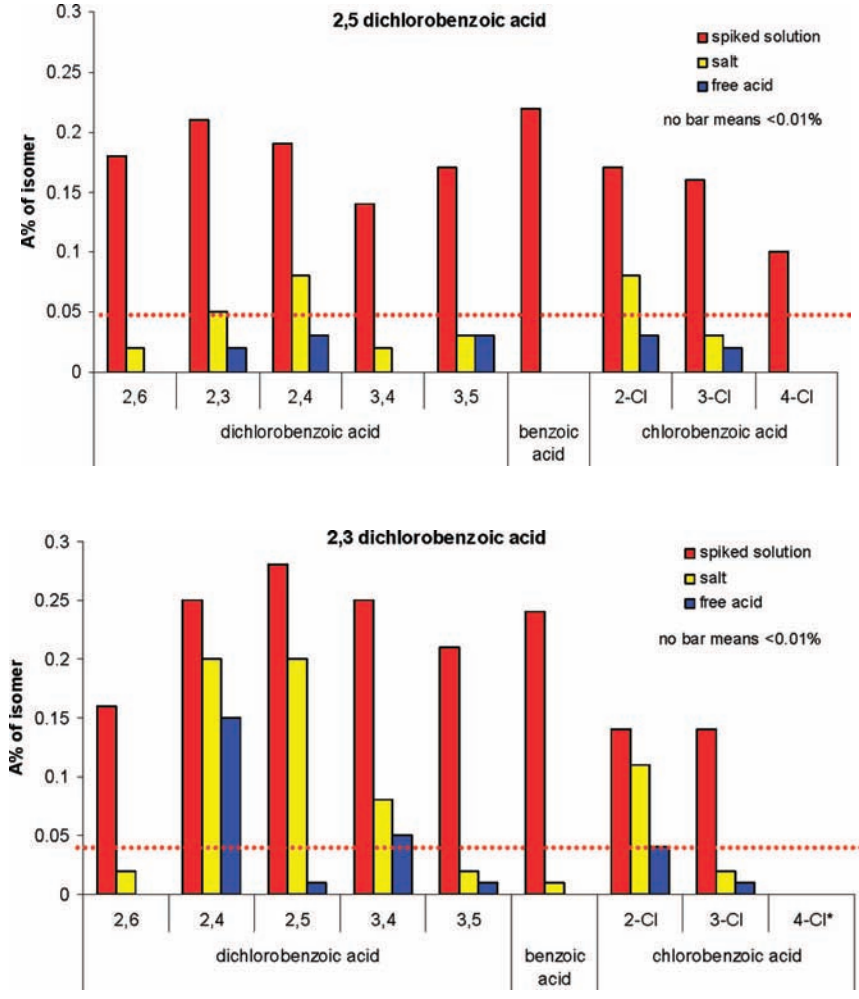
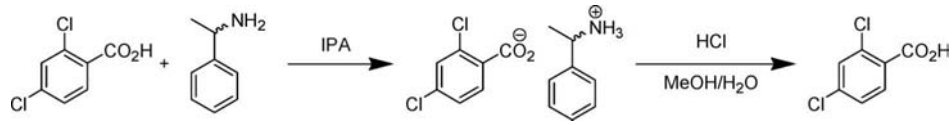


Figure 6. **Purification of other chlorobenzoic acids.**

Beyond the chloro-substituted benzoic acids, we were interested in the ability of this salt to purify other substituted benzoic acids. A similar screen of mono- and disubstituted, methyl and methoxybenzoic acids was

Scheme 2. **Purification of commercial DCBA**



conducted. An analogous process was effective at purifying 2,4-dimethoxybenzoic acid to <0.05%, as well as *m*- and *p*-toluic acids. Information on these screens can be found in the Supporting Information. Unfortunately, the high level of purification was not more general across these series, but again this salt may prove useful depending on which impurities are present.

Conclusion

An efficient purification process has been developed that can produce ultrapure DCBA through salt formation with (±)-α-methyl benzylamine. This process is operationally simple and uses inexpensive starting materials and benign solvents. This salt formation also purifies many other mono- and disubstituted benzoic acids. This high purity starting material translates into drug substance of consistently high quality without variation in the impurity profile.

Experimental Section

(±)-α-Methyl Benzylamine Salt of 2,4-Dichlorobenzoic Acid. 2,4-Dichlorobenzoic acid (10.0 g, 50.2 mmol) was dissolved in isopropyl alcohol (200 mL). The mixture was heated to 60 °C and (±)-α-methyl benzylamine (5.49 g, 45.3 mmol) was added all at once. The reaction was stirred at 60 °C for 1 h before the slurry was allowed to air-cool to room temperature. The product was isolated by filtration, and the wetcake was washed with isopropyl alcohol (25 mL). The product was dried in vacuo at 40 °C overnight. Yield 79%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (d, J = 7 Hz, 2H), 7.41 (s, 1H), 7.38 (qt, J = 10 Hz, 3H), 7.32 (t, J = 7 Hz, 1H), 7.28 (dd, J = 2, 6 Hz, 1H), 4.33 (qt J = 6.5 Hz, 1H), 1.49 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.9, 141.0, 140.8, 132.0, 131.0, 130.6, 129.0, 128.4, 127.1, 127.0, 50.3, 21.7; mp 185.2 °C (DSC).

2,4-Dichlorobenzoic Acid from the (±)-α-Methyl Benzylamine Salt. 2,4-Dichlorobenzoate-(±)-α-methyl benzylamine (5.0 g, 16.0 mmol) was dissolved in water (50 mL) and methanol (20 mL). The mixture was heated to 60 °C, and concentrated HCl was added until the pH was <2.0. The thick slurry was allowed to air-cool to room temperature. Water (12 mL) was added, the product was isolated by filtration, and the wetcake was washed with water (30 mL). The product was dried in vacuo at 40 °C overnight. Yield 94%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J = 8.6 Hz, 1H), 7.71 (d, J = 2 Hz, 1H), 7.51 (dd, J = 2, 6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.2, 136.9, 133.5, 132.8, 130.6, 130.5, 127.9; mp 162.0 °C (DSC).

Acknowledgment

The authors thank Anne Warner and Glenn McCain for analysis of samples.

Supporting Information Available

Graphs depicting the rejection efficiency of (±)-α-methyl benzylamine salts of various substituted benzoic acids are included. This information is availabkboprdle free of charge via the Internet at http://pubs.acs.org.

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(8) Similar rejection graphs are available in Supporting Information for the rest of the isomers.