Green Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2014, **16**, 3993

Optimization of the use of a chiral bio-based building block for the manufacture of DHPPA, a key intermediate for propionate herbicides

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Received 2nd May 2014,
Accepted 19th June 2014

DOI: 10.1039/c4gc00797b

www.rsc.org/greenchem

An alternative route for the production of (*R*)-2-(4-hydroxyphenoxy)propionic acid (DHPPA), a key intermediate in herbicide chemistry, is proposed. This route makes use of a chiral building block, initially produced by fermentation. The route has been optimized based on two steps: chlorination and etherification. The chlorination step has a maximum ee of 99% and a yield of 85% after distillation. The etherification step has a yield of 66%. Comparison of the route with the industrial standard shows a significant improvement in terms of green chemistry: waste streams are lowered up to 7-fold and the toxicity of the waste streams is reduced.

Introduction

"Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs".[1] This is the definition for sustainable development as put forward by Brundlandt in 1987. This definition can be applied both to green chemistry and to the securing of global food production with the aid of crop protection compounds. Roger Sheldon has been one of the pioneers in the past few decades emphasising the importance of green chemistry,[2] next to Anastas and Warner.[3] Sheldon's introduction of the *E* factor provides a powerful tool to assess the waste levels and thus the environmental impact of manufacturing processes in the chemical industry.[4] The *E* factor is simply defined as the actual amount of waste produced in the process, defined as everything but the desired product. Typically, this *E* factor is between 5 and 50 in the fine chemical industry and between 1 and 5 in the bulk chemical industry.[4] To meet the need of future generations, it is of paramount importance to improve the *E* factors for existing manufacturing processes.

Another important aspect of green chemistry is the use of sustainable raw materials.[5] The commercial production of bio-based building blocks has taken a flight in the past few years and compounds such as lactide,[6] succinic acid[7] and bio-ethanol[8] are produced with the aid of fermentation and are commercially available on a ton scale. The D- or (*R*)-enantiomer of lactic acid can be produced directly by fermentation and their esters are now readily available as well.[9]

Crop protection compounds clearly have shown their benefits by the reduction of labour requirements, the saving of fossil fuels, the improvement of food quality and the rise of crop yields.[10] The yield of fruits, vegetables and cereal crops is believed to drop between 32 and 78% if crop protection compounds were to be banned.[11]

The optimization of the production of crop protection compounds is an objective that serves both aforementioned trends. The manufacture of crop protection compounds (CPCs) generally involves multi-step synthesis, accompanied with *E* factors typical for the fine chemical and pharmaceutical industry.[4]

Progress in a greener approach to the production of fine and bulk chemicals is being established and also applied on an industrial production scale.[12] A famous example is the improved manufacturing of caprolactam by Sumitomo: the *E* factor goes down from 4.5 to 0.32, mainly because the improved process is salt-free.[13] Shell developed a process for the production of methyl metacrylate that reduces the *E* factor from 2.5 to almost zero.[14]

Diclofop-methyl was discovered in the 1970s as being effective in controlling grass weeds in field crops.[15] Following this, multiple herbicides were introduced with structural similarity and activity. This class of herbicides is currently known as the aryloxyphenoxypropionates (AOPPs or fops).[15]

In the HRAC (Herbicide Resistance Action Committee) classification in mode of action the AOPPs fall into category A: lipid synthesis inhibition or inhibition of acetyl-CoA carboxylase (ACCase). ACCase is an enzyme involved in the synthesis of fatty acids in plants.[16,17] The inhibition in the active site of

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the carboxyltransferase (CT) domain of ACCase by AOPPs leads to the termination of fatty acid synthesis, metabolic leakage and, ultimately, cell death.[18]

AOPPs are normally sold as esters. This is thought to improve handling and foliar uptake.[19] The actual active AOPP compound is the free acid, which is supported by X-ray studies with haloxyfop and clodinafop.[20,21] Activity studies have shown that the most active enantiomer of the AOPP herbicides is the (*R*)-enantiomer.[22,23] The increased activity of the (*R*) enantiomer has led to the production of enantiomerically pure AOPP herbicides. In their commercial names, this is usually designated with a P after the product name followed by the type of ester. For example: Quizalofop-P-ethyl is the ethyl ester of the pure (*R*) enantiomer of Quizalofop.

The manufacturing route of AOPP compounds usually proceeds through (*R*)-2-(4-hydroxyphenoxy)propionic acid (DHPPA) (Fig. 1). DHPPA is considered a key intermediate for AOPP industrial manufacturing. It is therefore necessary to be able to produce this compound with a high purity and cost effectively.

The existing industrial standard for preparing the DHPPA compound is by starting from (*S*)-alanine (Fig. 2). This route starts with the diazotization of the amine group followed by chlorination.[24] Overall, retention of configuration is obtained: the reaction proceeds by a double inversion through the unstable α-lactone. This results in (*S*)-2-chloropropionic acid (SCPA). Although this method is the current industrial standard, SCPA is known to be made *via* enzymatic dehalogenation of chloropropionic as well.[25] SCPA is subsequently condensed with hydroquinone using a William ether synthesis. In this reaction, inversion of configuration is observed and the desired DHPPA compound is obtained.[26]

From a green chemistry point of view, the main problem with this route lies in the chlorination step. A large waste stream is created during this reaction, because a work-up procedure that involves extraction is needed after the reaction.[24]

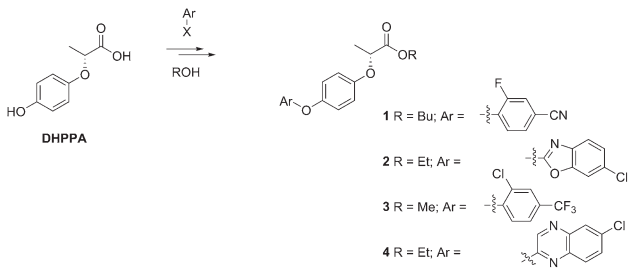

Fig. 1 Synthesis of cyhalofop-*p*-butyl (1), fenoxaprop-*p*-ethyl (2), fluazifop-*p*-butyl (3) and quizalofop-*p*-ethyl (4) from DHPPA.

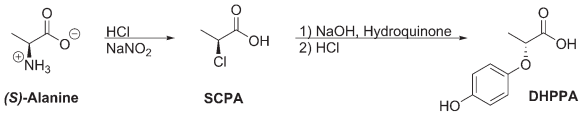

Fig. 2 Synthetic route towards DHPPA starting from (*S*)-alanine.

During the reaction, a stoichiometric amount of the highly toxic gas NO_x is separated from the reaction mixture. Next to the problems of toxicity and waste, the overall purity of the product faces limitations: a small but significant amount of racemization is observed and 95.6% ee is obtained, even when the starting material is >99.8% ee.[24] Summarizing, this route faces problems such as toxicity, excessive waste streams and limitations in product quality.

Here, we present an alternative route for the production of DHPPA that uses bio-based starting material, significantly improves the production process, lowers waste streams and delivers a higher quality product. We show that the use of ethyl (*R*)-lactate leads to the efficient production of DHPPA. We have optimized the chlorination of this lactate and reached an ee of 99%. The reaction to DHPPA is optimized to a yield of 66%. Besides, the proposed starting material is commercially available in sufficient quantities and we believe this process also delivers an economically feasible process.

Results and discussion

Chlorination of ethyl (*R*)-lactate

Seminal work on the chlorination of ethyl lactate has been published previously,[27,28] as well as the use of high amounts of CaF_2 as a catalyst.[29] However, to the best of our knowledge, a detailed optimization towards the high yield and enantiomeric purity shown *vide infra* has not been published before. The chlorination of ethyl (*R*)-lactate to ethyl (*S*)-chloropropionate (EtSCP) is shown in Fig. 3. EtSCP is then further reacted towards DHPPA. The ethyl (*R*)-lactate starting material was of very high quality and possessed an ee of >99.8%. The reactions were carried out under neat conditions. The chlorinating agent used was thionyl chloride. From a stereochemical point of view, an inversion takes place when alcohol is substituted by chloride. Reaction parameters such as catalyst type, catalyst loading, reagent stoichiometry and starting temperature have been altered systematically, to optimize this reaction for enantiomeric excess and overall yield. Besides that, the reaction has been optimized for handling on an industrial scale.

The results of the chlorination are shown in Table 1. As a control, the initial reaction was performed without a catalyst and a slight excess of thionyl chloride (entry 1). The reaction did not turn to completion. During the reaction, an extra compound was observed by GC. This compound increased at the initial stage of the reaction and decreased during the reaction. Therefore, this compound was considered a chemical intermediate. This intermediate is thought to be the sulfonate intermediate. Interestingly, the ee of the product was found to

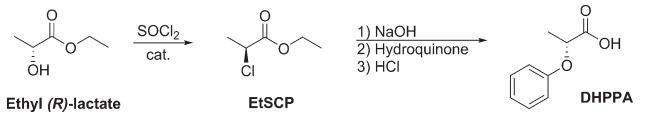

Fig. 3 Synthetic route towards DHPPA starting from ethyl (*R*)-lactate.

Table 1 Results on the chlorination of ethyl (*R*)-lactate

Entry	Cat.	$SOCl_2$ eq.	Cat eq.	*T* (°C) during $SOCl_2$ addition	GC profile of product (at%)			ee (%)	Crude yield (%)
					Et-SCP	Intermediate	Cl-ELL		
1	—	1.05	—	rt	84	16		92	93
2	pyr.	1.05	0.01	rt	98	2		79	95
3	pyr.	1.1	0.01	rt	100			85	93
4	pyr.	1.1	0.01	80	95		5	99	92
5	pyr.	1.1	0.10	80	95		5	92	—
6	dmf	1.1	0.01	rt	100			98	91
7	dmf	1.1	0.01	60	99		1	98	94
8	dmf	1.1	0.01	70	99		0.7	97	95[a]
9	dmf	1.1	0.01	65	95		4	98	Quant.

[a] Yield estimated by GC.

be 92% of the (*S*) enantiomer. Apparently, even without a catalyst, the reaction shows a high selectivity towards the right enantiomer.

The same reaction with pyridine as a catalyst (entry 2) showed that the reaction goes to further completion than without a catalyst, but still a residue of 2% intermediate was detected. Apparently, the catalyst performs a job similar to ethers added to the reaction mixture as reported previously.[30] The ee is lower than the blank reaction: 79%. The reaction was steered towards completion by increasing the amount of thionyl chloride (entry 3). The ee showed a slight increase as well, to 85%.

During the addition of thionyl chloride at rt, an exothermic process was observed and the temperature rose typically between 10 and 30 °C, depending on the experimental setup and batch size. To ensure a safe process at a larger scale, experiments were conducted where the temperature of the substrate during $SOCl_2$ addition was set between 60 and 80 °C. This temperature ensures the reaction to proceed in a controlled manner.

The initial temperature was set at 80 °C (entry 4). It was shown that the ee increased to 99%. This excellent result was confirmed *in duplo*. Another aspect of this reaction is the detection of a side-product. This side product was characterized by GC-MS and was confirmed to be ethyl chlorolactoyl propionate (Cl-ELL), the chlorinated dimer.[31] The formation of this product is hypothesized to be the result of transesterification: either the self-condensation of ethyl lactate or the reaction of EtSCP with ethyl lactate (Fig. 4).

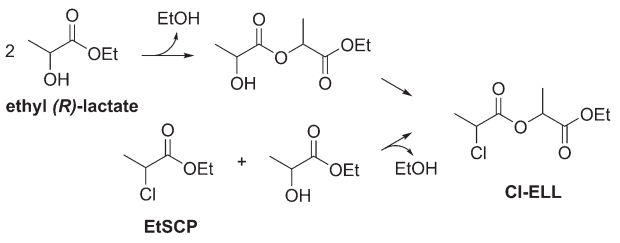

Fig. 4 Proposed reactions to Cl-ELL.

The influence of pyridine on this side reaction was studied, by increasing the catalyst load to 10%. No significant change was observed in terms of Cl-ELL formation. However, the ee of the product dropped to 92%.

Another well-known catalyst for chlorinations with thionyl chloride is dimethylformamide (dmf). At rt conditions, the reaction gave a full conversion towards the product and no side product or intermediate was observed. The ee can be considered high with 98%, but not as high as reached with the pyridine (entry 4). The safety precautions as mentioned *vide supra* compelled us to conduct these experiments at elevated temperatures. Addition at 60 °C showed minor formation of Cl-ELL (entry 7), but still a high ee with 98%. Increase to 70 °C did not show an increase in Cl-ELL formation and gave a consistent high ee.

The reaction was scaled up to 600 g (entry 9), as the other reactions were performed at a 30 g scale. The crude yield increased and the ee remained consistently high compared to the smaller-scale reaction. The formation of Cl-ELL, however, was increased in this case. A possible explanation for this is the prolonged time of thionyl chloride addition, compared to the smaller scale.

The crude yields of all reactions are above 90%. This crude yield is after an aqueous work-up. No difference in yield has been observed between the use of brine or distilled water. Although the purities of the crude product can be very high, even quantitative on GC, a yellow or amber colour can be observed in some cases. Therefore, the product was further purified with distillation.

Distillation of the batch shown in Table 1, entry 9 gave a yield of 84%. The purity of this product was 99.8 at%, the remaining 0.2 at% being Cl-ELL. The ee was preserved during distillation: no racemization was measured and the ee of the distilled product was 98%.

Production of DHPPA

The synthesis of (*R*)-2-(4-Hydroxyphenoxy)-propanoic acid (DHPPA) has previously been described in patent literature.[26] For this, EtSCP was first transformed into (*S*)-chloropropionic acid (SCPA).

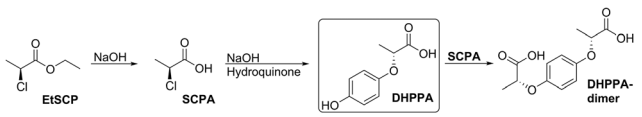

Fig. 5 Synthesis of DHPPA.

Table 2 Comparison of the chlorination of alanine with ethyl (*R*)-lactate

Entry	Feature	Alanine	Ethyl (*R*)-lactate
1	Yield (%)	60–70	84
2	Product purity (%)	95–99	>99
3	ee (%)	94–96	>99
4	*E* factor	7	1

The main problem of the DHPPA reaction as shown in Fig. 5 is the reaction with another SCPA molecule towards the DHPPA-dimer. This can possibly be suppressed by the increase of the amount of equivalents of hydroquinone.

The reaction with DHPPA has been done with 6.4 eq. of hydroquinone. Dimer formation was found to be approx. 4 at% on GC. The reaction gave a crude yield of 86%. Crystallization of the crude product in water gave a yield of 71%. This yield is significantly higher than found in the literature.[26,32] The excess of hydroquinone was conveniently recycled during work-up.

Waste streams and yields compared

The yields after work-up, product purity and enantiomeric purity of ethyl (*R*)-lactate chlorination have been compared with the analogous chlorination of (*S*)-alanine (Table 2, entries 1–3). We consider this a fair comparison for the synthesis of DHPPA, as follow-up chemistry towards DHPPA will hardly change.[33]

When the *E* factor is considered, the amount is 7 for the alanine route and 1 for the lactate route (Table 2, entry 4). The over 7-fold difference is mainly because of the use of solvents. The diazotization reaction must take place in aqueous hydrochloric acid,[24] whereas the chlorination of ethyl (*R*)-lactate with thionyl chloride is performed under neat conditions.

During the alanine chlorination, NO_x gas is expelled from the reaction. NO_x is known to cause acid rain.[34] Besides this, NO_x has a greater impact on the environment, as it is also involved in the production of ozone,[35] especially in the presence of salt mist.[36] Governmental regulations on NO_x are usually strict.[37,38]

Taking the waste stream and toxicity issues into consideration, it can be argued that the change in production of DHPPA with (*R*)-lactate esters is a significant step towards greener chemistry.

Experimental section

Materials and methods

Ethyl (*R*)-lactate is a Corbion Purac product. All other used reagents were obtained from Acros and were of analytical grade. GC chromatograms were taken on a Thermo Scientific Trace 1300 Gas Chromatograph equipped with a CP-Chirasil-Dex CB column, dimensions: 25 m, 0.25 mm, 0.25 μm. NMR spectra were recorded on a Varian 400 MHz instrument.

(*S*)-Ethylchloropropionate

Ethyl (*R*)-lactate (600 g, 5.08 mol) was put in a round bottomed flask together with dmf (3.71 g, 51 mmol, 0.01 eq.) under inert conditions and was heated to 65 °C. Thionyl chloride (665 g, 5.59 mol, 1.1 eq.) was added dropwise, during which gas was expelled from the reaction mixture and the temperature rose to 87 °C. After stirring for 4 h, no ethyl lactate was detected on GC and the reaction was complete. The reaction mixture was allowed to cool to rt and water (200 mL) was added dropwise. The temperature rose to 40 °C during the water addition. Brine (200 mL) was added and the layers were separated. The crude product was isolated as an orange liquid (698 g, quantitative yield). The crude product was distilled and the final product was obtained as a colourless oil (yield = 597 g, 86%, ee = 99%). Spectral data were in accordance with the literature.[28]

(*S*)-2-Chloropropionic acid (SCPA)

A 5 M aqueous NaOH solution was freshly prepared (85 mL 50% NaOH solution in 255 mL distilled water). This solution was put in a 1 L flask and ethyl (*S*)-2-chloropropionate was added dropwise. After 30 min the product was dissolved. The reaction mixture was stirred for another half hour and was cooled with ice and conc. HCl (177 mL) was added dropwise. DCM (250 mL) was added. The layers were separated and the organic layer was evaporated to dryness. The product was isolated as a colourless liquid (130 g, 85%) and used directly in the following step.

(*R*)-2-Hydroxyphenoxypropionic acid (DHPPA)

NaOH (51 g, 1.3 mol, 6.7 eq.) was dissolved in water (280 ml). After this, hydroquinone (134 g, 1.22 mol, 6.4 eq.) was added. The reaction mixture was stirred at ambient temperature. SCPA (20.6 g, 0.19 mol) was added and the reaction mixture was stirred at 72 °C; the conversion was checked regularly. After 3 h, the reaction was complete: no more CPA was detected. The reaction mixture was acidified with conc. HCl (aq) to pH = 6.0. The reaction mixture was washed with MIBK (3 volumes of 250 mL). The aqueous phase was further acidified to pH = 1.0 and extracted with MIBK (2 volumes of 150 mL). The organic layer was evaporated to dryness. The crude product was dried in an oven under vacuum at 40 °C and obtained as a light brown solid (30.7 g, 0.17 mol, 89% starting from SCPA). The crude product was dissolved in water (4 volumes) at 85 °C and the solution was slowly cooled to rt, crystallization was observed. The suspension was further cooled to 2 °C ± 1 °C and filtered over a büchi filter with a paper filter. The obtained crystals were washed with ice water (15 ml) and were dried at 60 °C under vacuum. The product was obtained as off-white crystals (19.0 g). The mother liquor was evaporated to dryness and dissolved in water (3 volumes) at 85 °C. The solution was slowly cooled to rt and no crystallization was observed.

Ent-crystals of the previous crystallization were added and crystallization was observed. The suspension was further cooled to 2 °C ± 1 °C and filtered over a büchi filter with a paper filter. Crystals were washed with ice water (1 volume). Crystals were dried at 60 °C under vacuum. The product was obtained as off-white crystals (3.9 g). Yield of crystallization: 1st and 2nd crystallization = 19.0 + 3.9 = 22.9 g, 74%; overall yield starting from SCPA: 22.9 g, 66%. Spectral data were in accordance with the literature.[39]

Conclusions

Optimization of a novel route towards DHPPA has been disclosed. The chlorination of ethyl(*R*)-lactate has been studied in detail. The formation of intermediates and side products has been minimized by adjustment of reagent stoichiometry, temperature and choice of catalyst. The highest ee (99%) was reached with the use of pyridine. The best overall result with a yield of 85% after distillation and still 98% ee was reached with the use of dmf at a starting temperature of 65 °C. These conditions are considered to be indicative for production on an industrial scale. The etherification towards DHPPA gave a yield of 66%.

In terms of green chemistry, significant improvements compared to existing practice have been made. We believe that the process presented here is economically feasible and even advantageous compared to current practice. The chiral starting material is a bio-based building block made through the process of fermentation. The further process has significant improvements in waste reduction and toxicity reduction. The resulting products are made with higher yields, higher selectivity and are of a higher quality compared to current practice.

Acknowledgements

We would like to thank Jan van Krieken and Kees van der Voort Maarschalk for useful discussions.

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