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One-pot Synthesis, Crystallization and Deracemization of Isoindolinones from Achiral Reactants

René R. E. Steendam[a], Michaël W. Kulka[a], Hugo Meekes[a], Willem J. P. van Enckevort[a], Jan Raap[b], Elias Vlieg*[a] and Floris P. J. T. Rutjes*[a]

Abstract: The synthesis, crystallization and solid-state deracemization of isoindolinones can be realized in one-pot simply by grinding achiral reaction components in a suitable solvent with an achiral catalyst. Previously, this concept was applied to a reversible reaction but herein we show that it can also be used in combination with reactions in which product formation is irreversible. A controlled final configuration of the product can be obtained using small amounts of chiral additives or seed crystals of the product.

Introduction

Single chirality in nature emerged under seemingly simple prebiotic conditions, yet the laboratory synthesis of enantiopure compounds under achiral circumstances still remains a formidable challenge to date. This challenge affects the chemical industry, which has to produce vast amounts of enantiopure building blocks for application in food and pharma products. The number of enantiopure drugs being launched is steadily increasing, so the development of novel methods to obtain enantiopure compounds is of paramount interest.[1] In addition, new processes need to be economical and sustainable, such as one-pot multistep conversions in which a combination of processes occur without intermediate recovery steps thereby reducing the number of unit operations.[2] An example of such a process is the *in-situ* transesterification and solid-state deracemization of the methyl ester of Naproxen in one pot.[3]

Recently, we reported an approach to reach single chirality in which two achiral reactants were transformed into an enantiopure product without pre-existing chirality (Figure 1).[4] During this process, the achiral enone and *p*-anisidine undergo a reversible aza-Michael addition in solution to give both enantiomeric β-amino ketones, which rapidly crystallize as racemic conglomerate crystals. These crystals repeatedly dissolve, racemize in solution and grow under grinding conditions and as such undergo deracemization through Viedma ripening.[5] Overall, this procedure encompasses a one-pot transformation involving three steps: 1) synthesis of the product from achiral reactants, 2) crystallization and 3) solid-state deracemization of the product under grinding conditions, after which the enantiopure product can simply be filtered from the solution. *In-situ* product precipitation can offer many advantages, for instance during continuous crystallization[6], an approach which already has led to the continuous resolution of crystals of threonine.[7]

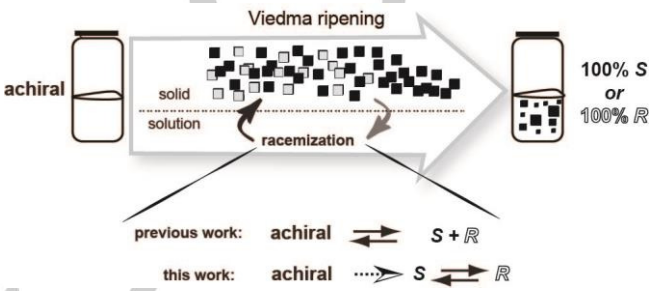

Figure 1. One-pot synthesis of enantiopure solids from achiral molecules. The previously reported racemization step involved only the reverse reaction.[4] This work involves two reactions: 1) irreversible product formation and 2) a racemization reaction of the product.

Key in the previous one-pot deracemization procedure is a reversible aza-Michael reaction, in which the combination and elimination of *p*-anisidine with an enone proceed under the same conditions, causing continuous solution phase racemization. A single reversible reaction thus leads to product formation as well as racemization in solution. However, in order to drive a reaction to completion, this reversibility must be avoided. Deracemization of such an irreversible reaction would still be possible only if racemization is induced through other means.

In this work, we use an irreversible reaction to make a chiral product and a reversible ring-opening and ring-closure reaction to induce racemization in solution. The irreversible reaction involves the formation of isoindolinones, a building block that might be used in the synthesis of a number of pharmaceutical drugs.[8] This one-way addition of achiral amines to achiral acid chlorides proceeds rapidly, leading to a racemic mixture of enantiomers. The isoindolinone products are not in equilibrium with the achiral precursors, but racemize in solution through an equilibrium of the N,O-acetal with the ring-opened form. After precipitation of the product, the crystals undergo deracemization through Viedma ripening. This way, three different isoindolinones were obtained in enantiopure solid form, from initially achiral conditions. The crystallization-induced absolute asymmetric synthesis concept can thus be extended to irreversible reactions.

Results and Discussion

The three isoindolinones **1**-**3** (Figure 2) crystallize as racemic conglomerate crystals, a property that is required to obtain molecules in enantiopure solid form.[9] In solution, the synthesis

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of isoindolinones **1-3** proceeds through the irreversible reaction of acid chloride **4** with the corresponding amine (Figure 2a). We found that this reaction can be promoted using DBU. Moreover, these molecules **1-3** undergo racemization in solution through a ring-opening and closing mechanism which can be induced by catalytic amounts of the same DBU.[9]

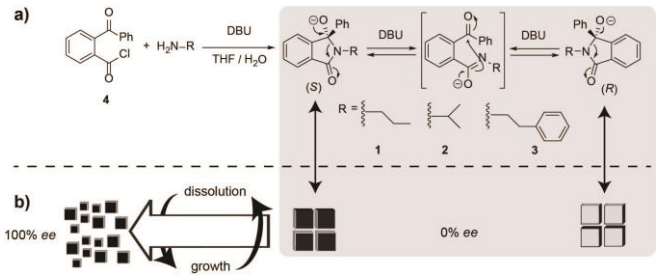

Figure 2. The one-pot transformation of achiral reactants into enantiopure isoindolinone crystals. a) In solution, the achiral precursor **4** reacts with the corresponding amine (H_2N-R) to give isoindolinones **1**, **2** or **3** which racemize through an achiral intermediate. b) Both enantiomers crystallize and undergo complete deracemization through Viedma ripening.

The combination of conglomerate crystallization and racemization in solution allows for the complete deracemization of isoindolinones **1-3** through total spontaneous resolution[9] or Viedma ripening (Figure 2b).[10] The synthesis of the isoindolinones from the corresponding precursors proceeds smoothly in THF in which the reactants and products readily dissolve. However, in order to combine the synthesis and deracemization of isoindolinones **1-3** in one-pot, precipitation of the product is required. Therefore, water was added prior to the experiment to enable precipitation of the product during the reaction. A typical experiment involves mixing of all the required achiral components (i.e. the acid chloride **4**, the corresponding amine, glass beads, DBU, the solvents THF and water and a stirring bar) into a round bottom flask. Once combined, the solution was stirred at full speed after which precipitation of the product started. The *ee* of the solids was monitored over time to show that an enantiopure solid state was obtained within two days for all three isoindolinones (Figure 3).

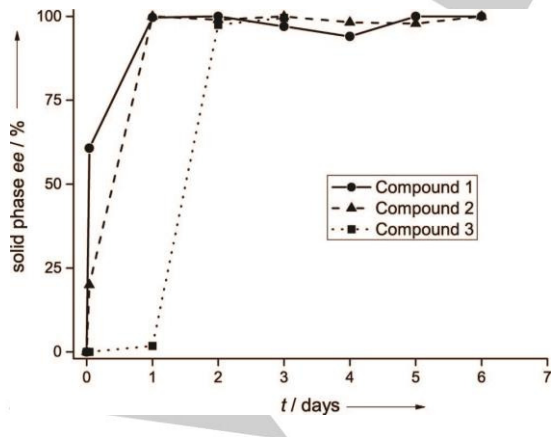

Figure 3. Evolution of the solid phase *ee* in time for all three isoindolinones.

To date, these isoindolinones were typically acquired through a homogenous solution-phase reaction after which quenching, multiple extractions, washing steps, drying, filtering, solvent removal and solid-state deracemization was needed to arrive at an enantiopure product.[9] With the herein reported protocol, these typical work-up procedures can be avoided as the enantiopure product can simply be isolated through filtration from the same flask in which the reaction took place.

The experiments reproducibly resulted in the complete transformation of achiral starting materials into the enantiopure products (Table 1). As these experiments start from achiral conditions, it is expected that the final configuration of the product is either (*R*) or (*S*) with equal probability. We found that enantiopure isoindolinone **1** was obtained 4 × (*R*) and 2 × (*S*) (entry 1). On the other hand, enantiopure isoindolinone **2** was more often obtained with a final (*S*) configuration (entry 2). The transformation of achiral reactants into enantiopure isoindolinone **3** proceeded to give 6 × (*R*)-**3** and 5 × (*S*)-**3**.

Table 1. Final configuration of the product depending on presence or absence of additves or seed crystals.

Entry	Isoindolinone	Additives / Seeds	Final configuration product[a]
1	**1**	-	4 × (*R*); 2 × (*S*)
2	**2**	-	2 × (*R*); 6 × (*S*)
3	**3**	-	6 × (*R*); 5 × (*S*)
4	**2**	(*S*)-**1**[b]	4 × (*R*); 1 x (*S*)
5	**1**	(*S*)-**1**[c]	5 × (*S*)
6	**3**	(*R*)-**3**[c]	5 × (*R*)

[a] The *ee* of the samples in each experiment was >99.9%. [b] 1.3 mol% of additive or c] 2.5 mol% of seed crystals were added right before stirring.

A non-stochastic outcome can be explained by the presence of chiral impurities which affect the crystal growth of one of the enantiomers.[11] The effect of chiral impurities can be overruled by using chiral additives that closely resemble the molecule that undergoes deracemization.[11] Isoindolinone **1** would be a suitable additive for the deracemization of isoindolinone **2** as these molecules crystallize in the same spacegroup (i.e. $P2_12_12_1$)[9] and are structurally similar. We indeed found that the addition of 1.3 mol% of (*S*)-**1** to give (*R*)-**2** in most experiments, following Lahav's rule of reversal[12] (entry 4). In a different way, (*S*)-**1** was reproducibly obtained using seed crystals of the same (*S*)-**1** (entry 5). The final configuration of isoindolinone **3** can also be controlled using seed crystals of the same product (entry 6). After filtration, white crystals of the product were obtained in about 55-74% yield and 97% *ee*. (see Supporting Information). DBU likely incorporates into the crystal structure of the product, resulting in trace amounts of DBU in the solid phase which can easily be removed through recrystallization. The mother liquor

consisted of only the product and DBU, which shows that no side reactions were involved during the experiments.

Conclusions

In conclusion, we here showed that the concept of crystallization-induced asymmetric synthesis of enantiopure products from achiral precursors can be extended to irreversible reactions. Our proof of concept involves the synthesis of three different enantiopure isoindolinones from the general reaction between an achiral acid chloride and achiral amine. This one-pot procedure was developed to allow racemization in solution and formation of conglomerate crystals, two requirements which enable complete deracemization of the solid state through Viedma ripening. The final configuration of the product could be controlled by enantiopure additives or more efficiently, using seed crystals of the desired product. Isolation of the product was simply achieved through filtration, which avoids many work-up steps that are otherwise required for this type of reaction.

Experimental Section

Typical procedure for the synthesis of enantiopure isoindolinones from achiral reactants in one-pot: Benzoyl chloride derivative **4** (1.25 mmol) was dissolved in THF (0.5 mL) in a roundbottom-flask (25.0 mL) which was filled with glass beads (7 g) and an octahedral stirring bar. The solubility of isoindolinone **3** was significantly lower than the solubility of isoindolinones **1** and **2**[10] and therefore a larger amount of THF (1.3 mL) was used for the synthesis of compound **3**. The solution was cooled using an ice bath and to the flask was added the appropriate amine (1.25 mmol), DBU (1.50 mmol) and water (1.0 mL). The resulting mixture was stirred at 600 rpm at room temperature and samples of the solids were collected through filtration and the *ee* was measured using chiral HPLC.

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Keywords: Chirality • Heterocycles • Chiral resolution • Synthesis design • Multicomponent reactions

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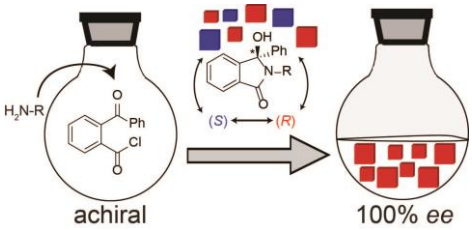

Synthesis of three enantiopure isoindolinones from achiral reactants is possible in one pot through solid-state deracemization which avoids the need for a chiral catalyst and work-up procedures.

Chiral resolution*

René R. E. Steendam, Michaël W. Kulka, Hugo Meekes, Willem J. P. van Enckevort, Jan Raap, Elias Vlieg and Floris P. J. T. Rutjes**

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