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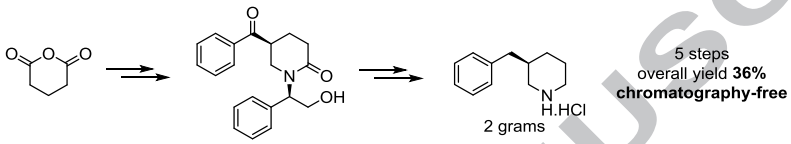

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ABSTRACT

The present study describes *aza*-Michael addition reactions of 4-aroylpent-4-enoic acids with (*R*)-phenylglycinol. Subsequent spontaneous lactamization yielded the corresponding piperidin-2-ones, which can selectively crystallize in very high diastereomeric purity. These are useful intermediates in the stereoselective syntheses of diverse 3-benzylpiperidines, as herein demonstrated by a chromatography-free and straightforward gram-scale synthesis of (*R*)-3-benzylpiperidine hydrochloride.

1. Introduction

3-Benzylpiperidine and its derivatives substituted at the aromatic ring have emerged as important structural subunits of potential drug candidates in pharmaceutical screenings.[1] In particular, (*S*)-3-(4-fluorobenzyl)piperidine was determined to be an integral part of several CC chemokine receptor-3 (CCR3) antagonists, e.g. **1**,[1e] **2** (DPC168),[1f] **3** (BMS-570520),[1g] **4** (BMS-639623)[1i] and **5**,[1j] with potential in the treatment of asthma (Figure 1).

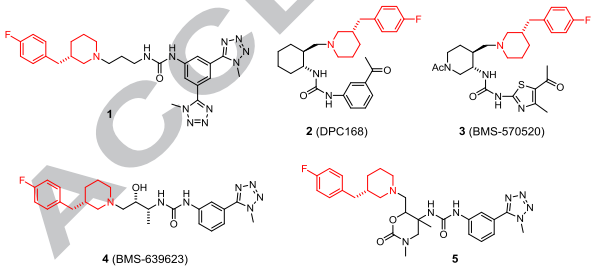
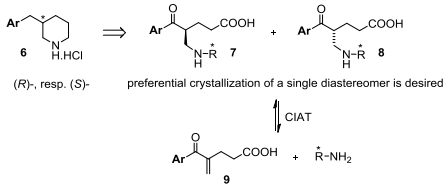


Fig. 1. Representative CCR3 antagonists containing the (*S*)-3-(4-fluorobenzyl)piperidine substructure.

In general, the CCR3 antagonists incorporating the opposite enantiomers of 3-benzylpiperidines exhibit differences in therapeutic potency. For the purpose of detailed activity studies and biological evaluation, a straightforward and reliable method for the stereoselective syntheses of diverse 3-benzylpiperidine derivatives are of great utility and interest.

Racemic 3-benzylpiperidines are synthetically accessible through reduction of pyridine derivatives,[2] Ru-catalyzed C-3 alkylation of *N*-benzylpiperidine[3] and by a tandem Ir-catalyzed *N*,*N*,*C*-trialkylation of *N*-phenylaniline.[4] As an alternative to an enantioselective synthesis, racemic hydrogenation of 3-alkylidenepiperidines[1e,5] and 3-alkylidenepiperidine-2-ones[6] were combined with subsequent optical resolutions. Stereoselective approaches towards 3-benzylpiperidines include stereoselective alkylations of piperidin-2-ones,[7] radical cyclisations of menthol-derived perhydro-1,3-benzoxazines[8] and asymmetric hydrogenations of 3-alkylidenepiperidine-2-ones[6,9] or 1,2,3,6-tetrahydropyridines.[10] However, due to their nature, each of the established stereoselective methods has certain limits in substrate scope and a complementary stereoselective synthetic route towards varied 3-benzylpiperidines might be of high value.

3-Acylacrylic acids have proven to be very good substrates for crystallization-induced asymmetric transformations (CIAT), yielding a variety of functionalized α-amino acids in excellent yields and stereoselectivities.[11-13] We envisioned that 4-aroylpent-4-enoic acids **9** in conjunction with *aza*-Michael additions might be utilized in a similar fashion, since they have structural features characteristic for known successful CIAT systems (Scheme 1).



Scheme 1. Considered synthetic strategy towards 3-benzylpiperidines **6** (**Ar** = aryl).

The presence of a free carboxylic functionality in substrates **9** increases the chances for obtaining a crystalline product, as

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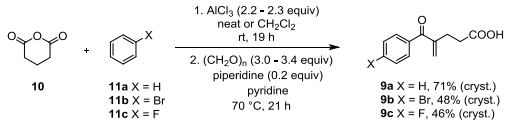
amino acids **7** and **8**, respectively, are formed in the course of the reaction. Moreover, *aza*-Michael additions are reversible, thus enabling a gradual shift of a reaction equilibrium in favour of a single diastereomer.

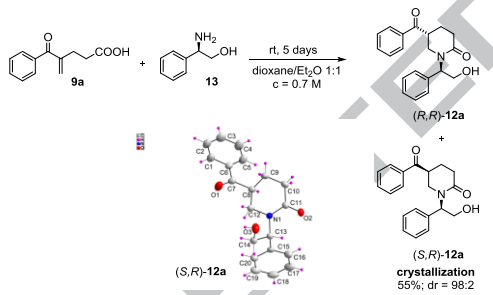
The starting 4-aroylpent-4-enoic acids **9a-c** were prepared based on a procedure reported for the synthesis of the homologous 3-(3-methylbenzoyl)but-3-enoic acid (Scheme 2).[14]



Scheme 2. Synthesis of 4-aroylpent-4-enoic acids **9a-c**.

With the aim of proving the concept, we embarked on exploring the reactivity of 4-benzoylpent-4-enoic acid **9a** with diverse primary amines. Encouragingly, reactions with (*S*)-alaninol and (*R*)-2-aminobutan-1-ol, both in 1,4-dioxane and CH_2Cl_2, resulted in precipitation of the corresponding amino acids within a few hours. However, equimolar mixtures of both diastereomers **7** and **8** were formed (dr ~ 1:1) and further screening of the reaction conditions did not lead to any improvement. Presumably, the formation of pseudoracemic crystals is favoured in this case, thus precluding crystallization-induced asymmetric transformation to a single diastereomer.[15]

Our alternative strategy was to develop a two-step, one-pot sequence yielding the corresponding crystalline piperidin-2-ones **12a**, which would subsequently undergo epimerization under CIAT conditions. The optimum reaction conditions turned out to be a combination of (*R*)-phenylglycinol **13** as the chiral auxiliary and a mixture of dioxane and Et_2O as the solvent (Scheme 3).



Scheme 3. Synthesis of piperidin-2-one (*S*,*R*)-**12a** and its crystal structure.

Under these conditions the target piperidin-2-one **12a** was formed as a mixture of two diastereomers (*R*,*R*)-**12a** and (*S*,*R*)-**12a**, in a 3:10 ratio. We were pleased to find that the major diastereomer preferentially crystallized out of the reaction mixture, furnishing piperidin-2-one (*S*,*R*)-**12a** as a white powder in a yield of 43% and an excellent diastereomeric purity dr > 99:1. Recrystallization of the mother liquour provided an additional 12% of (*S*,*R*)-**12a** in a dr = 95:5. The configuration of (*S*,*R*)-**12a** was unambiguously assigned by means of X-ray crystallography.[16] Unfortunately, we did not observe a change of dr values during the course of the reaction, i.e. CIAT was not involved and higher yields were out of reach. Our attempts to induce epimerization of the diastereomeric mixture by the addition of 20 mol% DBU, 3 equiv. NaOH, 2 equiv. HCl (4M sol. in dioxane) or 20 mol% piperidine/50 mol% acetic acid either failed or were incompatible with the crystallization of (*S*,*R*)-**12a**. On the other hand, although in a moderate yield of 55%, selective crystallization of (*S*,*R*)-**12a** as a single diastereomer noticeably simplified the isolation of this intermediate towards the synthesis of 3-benzylpiperidine.

We were intrigued by the possibility that this feature might be more general and applicable to a broader scope of substrates. Indeed, under analogous conditions (dioxane/Et_2O 1:1, c = 1.0 M, rt, 7 days) and starting from acid **9b**, we observed selective precipitation of 4-bromosubstituted derivative (*S*,*R*)-**12b** in a yield of 53% and dr = 96:4 (Figure 2).

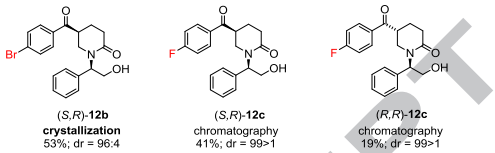
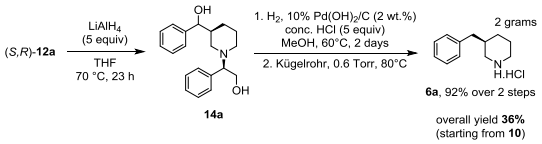


Fig. 2. Attempts towards selective crystallizations of piperidin-2-ones **12b** and **12c**.

This finding is of particular value since, if desired, the structure of (*S*,*R*)-**12b** opens up the possibility for further functionalization utilizing an array of coupling reactions. Unfortunately, the reaction system based on acid **9c** failed to deliver crystalline products and (*S*,*R*)-**12c** and (*R*,*R*)-**12c** had to be isolated by column chromatography.

The benefits of crystalline intermediates to the efficiency of a manufacturing process, avoiding tedious chromatographic purifications thus resulting in a striking waste reduction, has been recently shown in an "entirely non-chromatographic synthesis" of the Halaven C14-C26 fragment.[17] Herein, we demonstrate the utility of piperidin-2-ones **12** in a chromatography-free and straightforward gram-scale synthetic sequence towards (*R*)-3-benzylpiperidine hydrochloride **6a** (Scheme 4).



Scheme 4. Gram-scale preparation of (*R*)-3-benzylpiperidine hydrochloride **6a**.

Initially, piperidin-2-one (*S*,*R*)-**12a** was partially reduced with $LiAlH_4$, yielding a mixture of diastereomeric alcohols **14a**, in a ratio 5:1. These were directly used in the next hydrogenation step, smoothly affording (*R*)-3-benzylpiperidine hydrochloride **6a** contaminated with 2-phenylethanol. The impurity was removed *via* distillation under reduced pressure, furnishing the target compound as an off-white solid, in an overall yield of 36% for 5 steps, starting from glutaric anhydride **10**. Remarkably, neither of the reaction steps required chromatographic purification.

In summary, the present study describes a concise, practical and scalable stereoselective synthesis of (*R*)-benzylpiperidine hydrochloride **6a**. The synthesis completely avoids the use of chromatographic purification. A variety of additional structural modifications are potentially accessible *via* coupling chemistry of 4-bromosubstituted piperidin-2-one (*S*,*R*)-**12b** derivatives.

Acknowledgments

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Supplementary Material

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