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Regio- and stereoselective synthesis of polysubstituted 5-hydroxypyrrolidin-2-ones from 3-alkoxysuccinimides

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ABSTRACT

The synthesis of 4-ethoxy-5-hydroxypyrrolidin-2-ones and 6-hydroxyhexahydro-4*H*-furo[2,3-*c*]pyrrol-4-ones — through the regio- and stereoselective reduction of the corresponding 3-alkoxysuccinimides — is described. The reaction used $NaBH_4$ at low temperatures and short reaction times, providing products with yields of up to 77%. The stereoselectivity was highly influenced by both alkoxy and the *N*-moiety in the starting succinimide.

Introduction

The 5-hydroxypyrrolidin-2-ones — which are also known as hydroxy-γ-lactams, and have a succinimide ring as their main precursor — are cyclic amides that have a hydroxyl substituent at the 5-position of the heterocyclic ring. This class of compounds is notable due to the large variety of biologically active compounds containing the 5-hydroxypyrrolidin-2-one fragment, which has been isolated from natural sources. The simplest example of this class of compounds, 5-hydroxypyrrolidin-2-one, has been isolated from the fruit extracts of *Xanthium sibiricum* [1] and also from young leaves of the fern *Pteridium aquilinum* [2]. Similarly, compounds with a more complex structure (e.g., the structural analogues Fusarin C and Epolactaene — see Figure 1) have been isolated from strains of *Penicillium sp*. Considering that Epolactaene was the first active metabolite for the growth of neuronal SH-SY5Y human neuroblastoma cells, it became a reference compound for the synthesis of new active drugs against several neurodegenerative diseases [3].

Among the methods found in the literature for the synthesis of 5-hydroxypyrrolidin-2-ones, we highlight here the ones involving reactions of α,β-unsaturated ketones with cyanide ion [4–6], regioselective reduction reactions of succinimides using sodium borohydride [7–11] or Grignard reagents [12], and reactions from the expansion of the β-lactam ring involving the formation of the *N*-acyliminium ion as reactive intermediate [13,14]. Despite these aforementioned methods having been proven useful, some of them require an inert atmosphere and rigorous anhydrous solvents and laborious purification steps. With this in mind, in the last few years our research group has demonstrated the synthetic versatility of 4-alkoxyvinyl trihalomethyl ketones in the synthesis of pyrroles [15], tetrahydropyridines [16], pyrimidines [17,18], and several other aza/oxa heterocycles [19], including structurally related 5-hydroxy-5-(trifluoromethyl)pyrrolidine-2-ones [6] and pyrrolidine-2,5-diones [20] (see Scheme 1).

Given the fact that we have already reported the cyclocondensation reaction of 4-alkoxy-1,1,1-trihaloalk-3-en-2-ones with NaCN, which furnished CF_3-substituted 5-hydroxy-pyrrolidine-2-ones [6] and the unexpected preparation of 4-cyanocarboxylic acids and further cyclization to pyrrolidine-2,5-diones [21] (Scheme 1), we now wish to report the asymmetric reduction of these 3-alkoxysuccinimides (3-alkoxypyrrolidine-2,5-diones) with

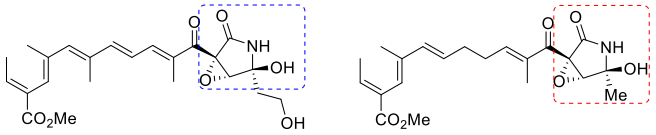

Figure 1. Bioactive natural products containing the fragment 5-hydroxypyrrolidin-2-one.

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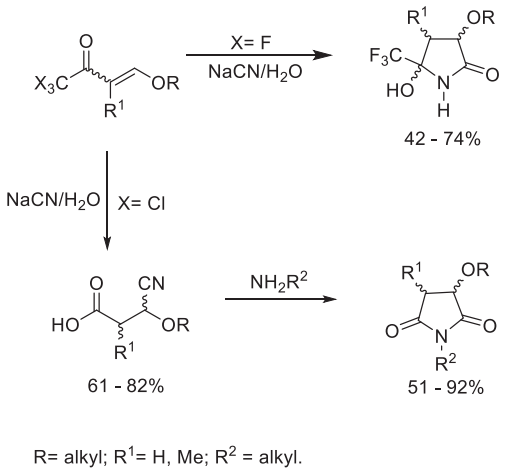
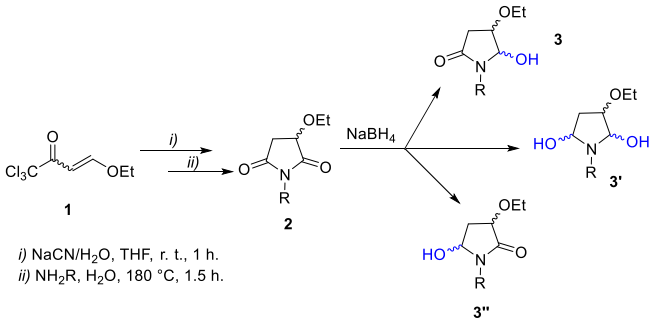


Scheme 1. Synthesis of 5-hydroxy-5-(trifluoromethyl)pyrrolidin-2-ones and pyrrolidine-2,5-diones.



Scheme 2. Synthetic approach to the synthesis of succinimides **2**, and products that could possibly be obtained from the reduction with $NaBH_4$.

a hydride source. Despite the fact that the addition of common hydride sources (e.g., $NaBH_4$, $LiAlH_4$, and $NaBH_3CN$) to carbonyl compounds are not selective reactions, they are highly influenced by the reaction conditions (temperature and solvent used) and steric effects of the substrate, providing stereo- or *enantio*-enriched products [22–29].

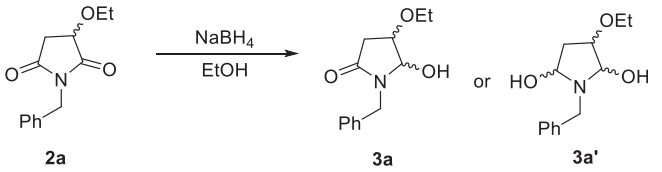
Scheme 2 comprises the synthesis of succinimides **2** from 1,1,1-trichloro-4-ethoxybut-3-en-2-one **1**, and the possible products from the reduction of succinimides **2** with $NaBH_4$, in which single (**3**, **3''**) or double reduction can occur (**3'**).

Results and discussion

Initially, 1,1,1-trichloro-4-ethoxybut-3-en-2-one was prepared from the trichloroacetylation reaction of ethyl vinyl ether, in accordance with the method previously reported [30]. Preparation of the corresponding 4-cyanocarboxylic acid, as well as posterior cyclocondensation with amines to furnish the succinimide derivatives, was done in accordance with previous studies [20,21].

We considered succinimide **2a** for optimization of the reaction conditions, and ethanol as solvent, using conditions adapted from elsewhere [22]. It is important to note that during this step we did not observe the selective reduction of the carbonyl at the 5-position of the starting **2a** — only the mono-reduced (at the 2-position of the starting **2a**) and di-reduced forms were obtained. Table 1 shows the results obtained and, one can clearly see that the reaction is quite sensitive to small changes (e.g., greater amounts of $NaBH_4$ furnished a mixture of **3a** and **3a'**). Small amounts (4, 3, and 2 equiv) were used, but all tests furnished the mixture of

Table 1
Optimization of reaction conditions for the selective reduction of **2a**.



Entry	$NaBH_4$ (equiv.)	Temp. (°C)	Time (min)	Product	Yield (%)[a]
1	5	−30	30	**3a + 3a'**	-[b]
2	5	−30	15	**3a + 3a'**	-[b]
3	1.2	−30	15	**3a**	70
4	1.2	−30	30	**3a**	71
5	1.0	−30	15	**3a**	51
6	1.2	25	15	**3a + 3a'**	-[b]

Reaction conditions: **2a** (1 mmol), $NaBH_4$, EtOH (3 mL). [a] isolated yield. [b] not determined.

mono- and di-reduced products. Feasible results were obtained when using 1.2 equiv of $NaBH_4$ (Table 1, entry 3), which provided **3** as a single product with an isolated yield of 70% after 15 min of reaction. The product was purified by filtration over Al_2O_3, using ethyl acetate as solvent.

Having controlled the reaction to provide only the single-reduced product, we next explored the regioselectivity of the reaction. Given that product **3a** has two asymmetric centers, it would be expected to be obtained as a mixture of stereoisomers — both *anti* and *syn* are shown in Figure 2. The diastereoisomeric composition was determined by GC–MS, and, for compound **3a**, we observed a ratio of 4:1 *anti*/*syn* (Figure 2).

With the optimized conditions in hand, and having determined the diastereoisomeric ratio, we next explored the reaction scope by varying the R substituent in starting succinimide **2** (Table 2). All products were obtained at moderate to good yields (54–77%) — the higher diastereoisomeric ratio was obtained when R = benzyl, providing a ratio of 4:1 *anti*:*syn* (Table 2, entry 1). Similar substituents (R = CH_2Py, $(CH_2)_2Ph$) provided ratios in the range of 2:1. Surprisingly, when R = Et, only the *anti* diastereoisomer was observed. Other alkyl substituents were used but provided a diastereoisomeric ratio too low to be feasible; therefore, they are not shown here. The compounds were obtained in their pure forms after column chromatography — see Supporting Information for more details. The *syn*-isomers could not be recovered as pure compounds from the chromatographic method used. Table 2 shows the diastereoisomeric ratio of products 3 (determined either by GC–MS or by ^1H NMR integrals) and the isolated yield of the mixture.

In order to evaluate the influence of the ethoxy substituent at the 3 position of the succinimide ring, we subsequently changed the substrate to a succinimide-tetrahydrofuran bicycle **5** (tetrahydro-5*H*-furosuccinimides — see Scheme 3). Unlike the reduction reactions of 3-ethoxysuccinimides **2**, in which a mixture of

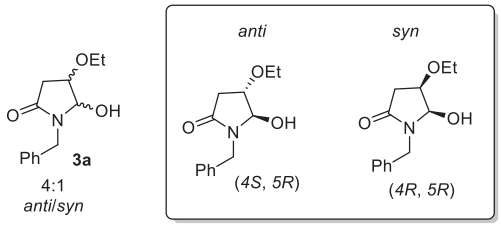
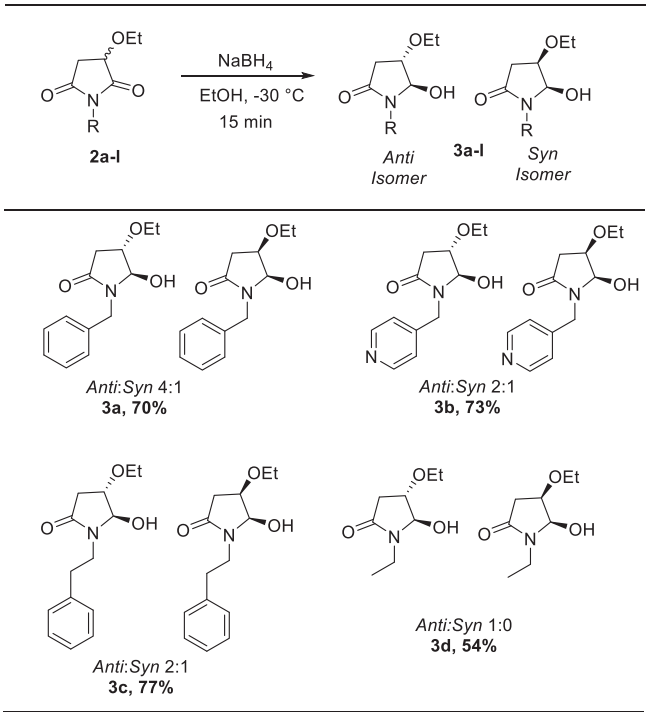
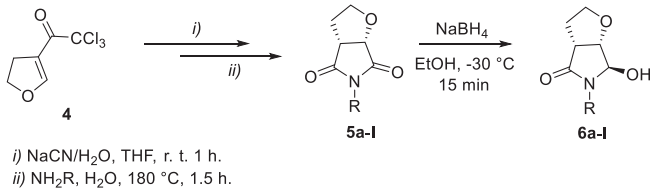


Figure 2. Schematic representation of the *anti* and *syn* stereoisomers for compound **3a**.

Table 2
Reaction scope of the reduction reaction by varying the starting succinimide **2**. The isomer proportion was determined either by GC–MS or ^{1}H NMR integrals.





Scheme 3. Approach towards the synthesis and posterior selective reduction of succinimides **5a**–**l**.

diastereoisomers was obtained (except for **2i**), in this stage, only one diastereoisomer was observed when using tetrahydro-5*H*-furosuccinimides **5**. There are two major reasons for the observed selectivity: i) the cyclization reaction of 4-cyanocarboxylic acid (obtained from the reaction of compound **4** with NaCN, Scheme 3) with amines providing only the *syn* diastereoisomer — thus, the product would be already stereoselected before the reduction with $NaBH_4$; [20] and ii) the replacement of the ethoxy group at position-3 with the fused furan heterocycle provides greater selectivity, due to steric effects caused by the cyclic furan instead of the flexible ethoxy group.

By reacting succinimides **5** with $NaBH_4$, under the same experimental conditions as described for the synthesis of products **3**, we observed low to moderate yields (27–65%) for the synthesis of **6**, depending on the starting succinimide. Given that some low-yielding products were obtained, we increased the reaction time to 1 h; however, the yield did not increase considerably. By adding more equiv of $NaBH_4$ (1.5, 2.0), a mixture of mono- and di-reduced products was observed in the ^{1}H NMR spectra. Table 3 shows the reaction scope for the selective synthesis of fused furan-pyrrolones **6**.

Figure 3 shows dihedral angles and the related coupling constants of representative compounds **3a** and **6a.** The dihedral angles

Table 3
Reaction scope for the reduction of succinimides **5**.

Entry	Succinimide	R (Amine)	Product	Yield (%)[a]
4	**5a**	-$CH_2C_6H_5$	**6a**	65
1	**5b**	–CH_2-2-Py	**6b**	61
2	**5c**	–CH_2-3-Py	**6c**	57
3	**5d**	–CH_2-4-Py	**6d**	42
5	**5e**	-$(CH_2)_2C_6H_5$	**6e**	40
6	**5f**	-$(CH_2)_2NMe_2$	**6f**	27[b]
7	**5g**	-$(CH_2)_2NEt_2$	**6g**	57[b]
8	**5h**	Me	**6h**	32
9	**5i**	Et	**6i**	61
10	**5j**	Pr	**6j**	60
11	**5k**	*i*-Pr	**6k**	38[b]
12	**5l**	Allyl	**6l**	46

[a] Isolated yield. [b] Product isolated with non-identified impurities.

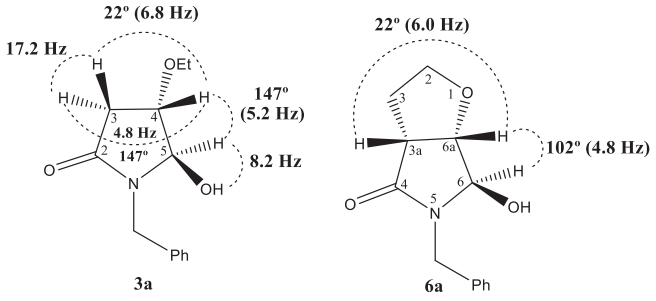


Figure 3. Three-dimensional structures of compounds **3a** and **6a**, showing dihedral angles and the related coupling constants.

were obtained from theoretical minimization energy from standard AM1 calculation. One can see that the dihedral angle between the *syn*-hydrogens (H3 and H4) of compound **3a** was 22° — the same dihedral angle as that between the H3a and H6a of the rigid compound **6a**. The experimental coupling constants for this dihedral angle were 6.8 and 6.0 Hz for compounds **3a** and **6a**, respectively. The dihedral angle of the *anti*-hydrogens (H3 and H4) of the compound **3a** is 147° and for the compound **6a** the *anti*-hydrogens (H6 and H6a) is 102°. The coupling constant observed for these dihedral angles was 4.8 Hz for both compounds. Taking these values for the dihedral angles and coupling constants as the basis for determining the possible configuration of carbons 4 and 5 of compound **3a**, one can state that the configurations of these two compounds are *anti*, because they presented comparable coupling constants of 5.2 and 4.8 Hz. Therefore, the alkoxy and hydroxy moieties are in *anti*-configuration for the main isomer of compounds **3** as well as for the rigid products of compound **6**.

Conclusion

In summary, we presented a regio- and stereoselective reduction protocol for the synthesis of 4-ethoxy-5-hydroxypyrrolidin-2-ones and 6-hydroxyhexahydro-4*H*-furo[2,3-*c*]pyrrol-4-ones, which was accomplished by using $NaBH_4$ at low temperatures and short reaction times, providing products with yields of up to 77%. By controlling the reaction conditions, only the carbonyl neighboring the alkoxy group was reduced. Regarding the regioselectivity of the reductions, the ethoxysuccinimides furnished predominantly *anti*-configuration products; while for the tetrahydro-5*H*-furosuccinimides, only the *anti*-product was observed. It was observed that the stereoselectivity of the reduction was highly influenced by both the alkoxy and *N*-moiety in the starting succinimide.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151358.

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