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Improved procedure for the enantioselective synthesis of dihydrooxazolo and dihydrothiazolo ring-fused 2-pyridones

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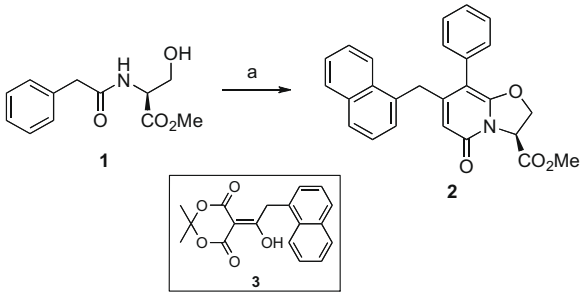
ABSTRACT

Improved procedures to synthesize enantioselectively analogues of a peptidomimetic scaffold with high biological relevance have been developed. Experimental design led to a general method for the preparation of dihydrooxazolo ring-fused 2-pyridones in good yields and high enantiomeric purity. The knowledge gained from this was also used to improve the microwave-accelerated synthesis of dihydrothiazolo ring-fused 2-pyridones to give complete stereo retention and high yields.

Development of bacterial resistance is an ongoing process that poses a major health threat to modern society.[1,2] As a consequence, new strategies to treat bacterial infections are needed. Targeting bacterial virulence factors is one such strategy that would reduce the ability of bacteria to cause infection without threatening its survival.[3–5] Pilicides and curlicides are compounds, based on the same peptidomimetic scaffold, that target bacterial virulence factors in Gram-negative bacteria.[6–8] The pilicides act by preventing the formation of pili on the bacterial surface whereas the curlicides target the formation of another type of bacterial fibre, termed curli, which are functional amyloids. The common pilicide and curlicide peptidomimetic scaffold consists of a dihydrothiazolo ring-fused 2-pyridone structure that is commonly synthesized via an acylketen-imine cyclo-condensation.[9,10] Studies of this scaffold are particularly interesting for its direct applicability in the synthesis of pilicides and curlicides, and also for its more general use as a peptidomimetic towards other biological targets. In a recent study it was shown that the sulfur in the scaffold could be exchanged for oxygen with an almost retained pilicide activity.[11]

Unfortunately the reaction conditions for this method also epimerized the stereogenic centre at position C-3 in the scaffold **2** (Scheme 1). As control of stereogenic centres is of significant importance for a heterocyclic scaffold to be useful as a peptidomimetic, we decided to search for new reaction conditions where the focus was to achieve reasonable isolated yields with high optical



Scheme 1. Reagents and conditions: (a) (i) 10 mol % $(NH_4)_2MoO_4$, toluene, Soxhlet, 3 Å MS; (ii) addition of acid (TFA), **3**.

purity. Therefore, to determine the optimal reaction conditions, experimental design was used.[12] The reaction time, acidity and number of equivalents of acid were regarded as influential factors for the outcome of the reaction. The choice of acid is ambivalent; it should catalyze the acylketen-imine cyclo-condensation but still not epimerize the stereogenic centre in the final ring-fused product. Thus, one stronger acid and one weaker acid, as compared to the previously used TFA, were chosen. In addition, the use of high boiling acids would be advantageous because the reaction is performed in refluxing toluene in order to remove effectively the water generated in the 2-pyridone forming step. Consequently, by varying the acid, reaction time and equivalents of acid, while measuring the yield and enantiomeric excess as responses, a D-optimal design[13] with eight experimental runs was created using

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Table 1
Results from the experimental design

Entry	Exp. No.	Acid	Equiv	Time (h)	Yield[a] (%)	ee[b] (%)
1	1	MP-TsOH	0.1	4 + 2	0	0
2	2	MP-TsOH	5	4 + 1	0	0
3	3	PPTS	0.1	4 + 2	41	99
4	3	PPTS	0.1	4 + 2	57	93
5	4	PPTS	5	4 + 1	56	92
6	5	*p*TsOH	0.1	4 + 1	36	92
7	5	*p*TsOH	0.1	4 + 1	57	88
8	6	*p*TsOH	5	4 + 2	0	0
9	7	TFA[c]	0.1	4 + 1	28	91
10	8	TFA[c]	5	4 + 2	78	2

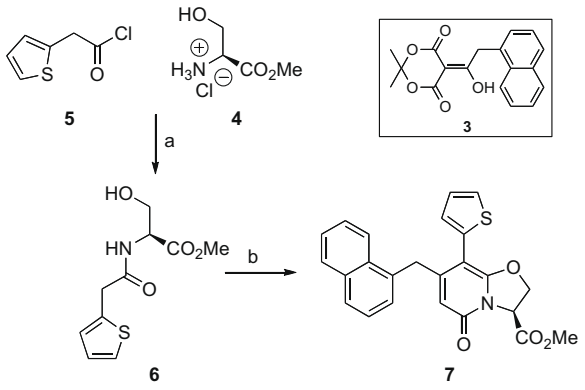
Eight experiments and two replicates were run. The enantiomeric excess was determined by chiral HPLC using a WHELK-O 1 column.
[a] Isolated yield.
[b] Determined using chiral HPLC.
[c] Previously collected data.[11]

the chemometric software MODDE 8.0. In total ten experiments, eight plus two replicates, were performed and the results are shown in Table 1.

From these data the type and amount of acid proved to be the most influential factors on both the yield and enantiomeric excess whereas the reaction time seems to be of less importance. The use of polymer-bound tosic acid, MP-TsOH, gave no product, probably due to the poor swelling properties of the polystyrene in toluene. 2-Pyridone **2** synthesized using pyridinium *p*-toluenesulfonate (PPTS) resulted in an excellent enantiomeric excess (92–99%) and was isolated in 41–57% yield. The use of 0.1 equiv of *p*TsOH gave 36–57% yield of **2** with 88–92% enantiomeric excess. However, the use of 5 equiv of *p*TsOH resulted in a complex reaction mixture containing several unidentified byproducts and no 2-pyridone **2** could be isolated.

PPTS can be readily prepared from pyridine and *p*-toluenesulfonic acid monohydrate, is easy to handle and can be stored under anhydrous conditions.[14] This made additional screenings to further optimize the reaction conditions excessive and the use of catalytic amounts of PPTS in refluxing toluene was considered to be the conditions of choice for the synthesis of the oxygen analogues of the peptidomimetic scaffold.

To verify that the optimized conditions were applicable to other substrates, a thiophene-substituted compound **7** was synthesized. The starting material **6** was prepared from methyl ester protected serine **4** and thiophene acetyl chloride (**5**) in 81% yield. Subsequent treatment of **6** using the developed conditions resulted in the formation of the dihydrooxazolo ring-fused 2-pyridone **7** in 71% yield and 95% enantiomeric excess (Scheme 2).

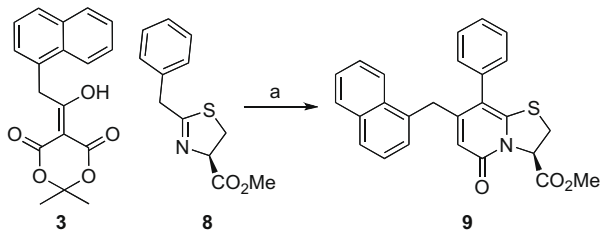


Scheme 2. Reagents and conditions: (a) Et_3N, CH_2Cl_2, −8 °C to rt, 3 h, 81% yield; (b) (i) 10 mol % $(NH_4)_2MoO_4$, toluene, Soxhlet, 3 Å MS, reflux; (ii) PPTS, **3**, toluene, Soxhlet, 3 Å MS, reflux, 71% yield, 95% ee.

Having established conditions for the acid-sensitive formation of dihydrooxazolo ring-fused 2-pyridones, we next examined if the use of PPTS as acid source would also be applicable in the synthesis of the dihydrothiazolo ring-fused 2-pyridone scaffold. This could be beneficial for the introduction of sensitive functional groups and it might also make the synthesis of dihydrothiazolo ring-fused 2-pyridones in high enantiomeric excess more convenient. Previously the high enantiomeric excess could be obtained by using partly HCl-saturated solvent mixtures, however, the solvents were troublesome to prepare, almost impossible to store and most importantly, gave inconsistent results. In 2006, Pemberton et al. showed that it was possible to perform the acylketenimine cyclo-condensation using TFA as the acid.[15] As a consequence, the use of this more reliable and easily handled acid for the synthesis of dihydrothiazolo ring-fused 2-pyridones has been used subsequently without a detailed knowledge about its effect on the enantiomeric excess. Therefore, the effect of TFA, using the standard conditions, on the enantiomeric excess and the possible use of PPTS in the synthesis of dihydrothiazolo ring-fused 2-pyridone **9** was studied. Using the standard conditions, microwave irradiation of **3** and **8** at 120 °C for 140 s with one equivalent of TFA in 1,2-dichloroethane,[7] gave **9** in 93% yield. However, this was also accompanied with an 11% drop in enantiomeric excess. Reducing the amount of TFA to 0.2 equiv increased the enantiomeric excess (93%), but this also reduced the yield to 64% (Table 2). Using the same conditions but changing the acid to 0.2 equiv of PPTS left the stereogenic centre unchanged while still giving an 86% yield. Finally, increasing the amount of PPTS to one equivalent increased the yield further (96%) and also the stereogenic centre was unaffected (Table 2).

In conclusion, an improved enantioselective synthesis of dihydrooxazolo ring-fused 2-pyridones has been developed. The use of the experimental design led to a general method that allows the preparation of dihydrooxazolo ring-fused 2-pyridones in excellent enantiomeric excess and good yields. In addition, these conditions could also be converted to the microwave-accelerated synthesis of dihydrothiazolo ring-fused 2-pyridones with complete stereo retention and high yields. The methods developed herein should substantially facilitate the synthesis of dihydrooxazolo and dihydrothiazolo ring-fused 2-pyridones in high enantioselectivity and yield, in terms of both reliability and applicability. This is important in the continued search for new antivirulence compounds in particular, but it is also of interest for the future use of these optically active peptidomimetic scaffolds in general.

Table 2
Synthesis of dihydrothiazolo ring-fused 2-pyridones in high yields and with high stereo retention



Acid	Equiv	Yield[b] (%)	ee **8** (%)	ee **9** (%)	Δ ee[c] (%)
TFA	1	93	95	84	11
TFA	0.2	64	95	93	2
PPTS	0.2	86	95	95	0
PPTS	1	96	95	95	0

[a] Acid, 1,2-dichloroethane, MWI: 120 °C, 140 s.
[b] Isolated yield.
[c] Difference in enantiomeric excess between Δ^2-thiazoline and 2-pyridone.

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Supplementary data

Supplementary data (experimental procedures for the preparation of **2**, **6**, **7** and **9**, NMR spectra for compounds **6** and **7**, and HPLC chromatograms for enantiomeric excess determinations) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.162.

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