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SHORT COMMUNICATION

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Concise Preparation of Optically Active Heteroaryl α-(Hydroxyamino) Esters

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A practical sequence for the synthesis of optically active heteroaryl α-(hydroxyamino) esters was explored. The highly diastereoselective addition of heteroaromatics to a cyclic chiral nitrone allowed access to a series of heteroaryl hydroxylamines. The scope of this reaction was evaluated on substrates possessing a pyrrole, an indole, or a furan core. The three-step sequence afforded the α-(hydroxyamino) esters in good overall yields (36–62 %) with good enantiomeric excess values (76 to ≥98 %).

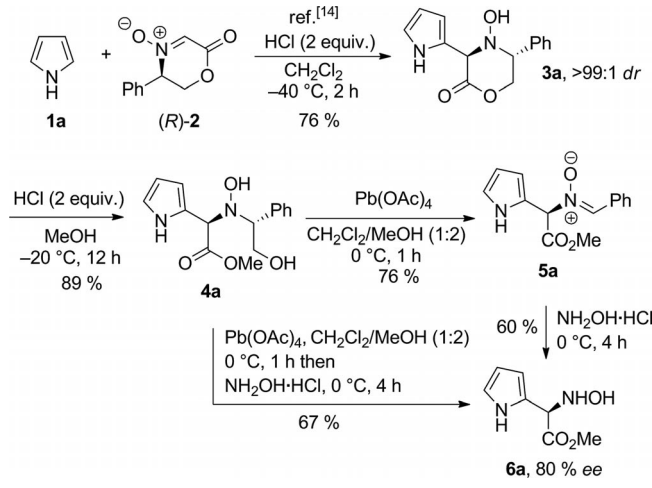
Introduction

α-(Hydroxyamino) acids are present in many natural products[1] and pharmaceutical compounds.[2] Whereas the synthesis of optically active α-amino acids is well established,[3] only a few research groups have succeeded in the preparation of the analogous α-(hydroxyamino) acids. This may be impeded by the reported instability of these compounds,[4] which therefore necessitates the protection of the carboxylic acid function,[5] the hydroxylamine function,[2,6] or both.[7] The enantioselective hydrolysis of amides containing hydroxyamino acid moieties by L-selective amidases has also been studied, but only for amides derived from either racemic *N*-hydroxyphenylglycine[8a] or *N*-hydroxyphenylalanine.[8b]

In previous work, our group reported the nucleophilic addition of pyrroles and indoles to the C=N bond of nitrones to afford hydroxylamines in good yields.[9] In this context, we decided to focus on the preparation of optically active heteroaryl α-(hydroxyamino) esters.[10] The preparation of this class of compounds is a challenge for organic chemists, taking into consideration the difficulty to obtain enantiomerically enriched products. Indeed, owing to the presence of the acidic α-methine proton, rapid epimerization can occur, which is similar to aryl and heteroaryl amino esters.[11] Despite their relatively simple structures, only a few examples of racemic *N*- or *O*-alkylated pyrrole derivatives have previously been reported.[12]

Results and Discussion

The addition of pyrrole (**1a**) to cyclic chiral nitrone (*R*)-**2**[13] was highly diastereoselective and led to the exclusive formation of (3*R*,5*R*)-**3a** in 76% yield.[14] Compound **3a** was next converted into α-(hydroxyamino) ester **6a** in only a few steps (Scheme 1). Our synthetic plan for the preparation of α-(hydroxyamino) ester **6a** implied the oxidative cleavage of the β-alkoxy hydroxylamine moiety. Unfortunately, this reaction proved to be unsuccessful starting from cyclic **3a** in the presence of lead tetraacetate. This derivative was thus transformed into open-chain hydroxylamine **4a** by acid-catalyzed transesterification. In the presence of lead tetraacetate,[15] the oxidative cleavage of **4a** pleasingly gave expected nitrone **5a** as a unique regioisomer. The final hydroxyaminolysis led to pyrrolyl hydroxyamino ester **6a** in 60% yield. The overall yield could be improved by performing the last two steps in a one-pot sequence



Scheme 1. Synthetic pathway to hydroxyamino ester **6a**.

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[‡] Dedicated to the memory of our colleague and friend Dr. Nadia Pelloux-Léon who passed away on February 22, 2014

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(Scheme 1). Under these conditions, **6a** was obtained in 80% enantiomeric excess (*ee*, measured by HPLC on a chiral stationary phase).[16]

This synthetic route was next extended to a variety of heteroaromatic compounds. Pyrroles **1b–e**, indoles **1f–g**, and 2-methylfuran **1h** (Figure 1) seemed to be a suitable series for the starting materials. Indeed, these substrates cover a representative range of π nucleophilicity, as previously reported by Mayr and co-workers for other C–C bond-forming processes.[17]

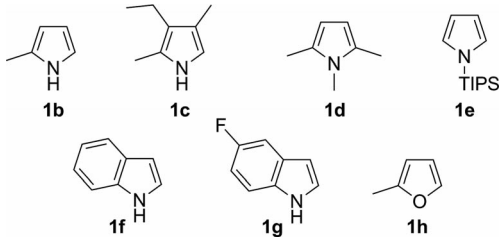


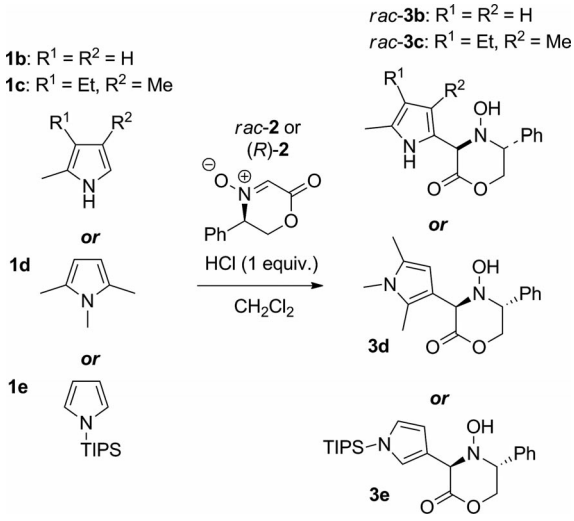
Figure 1. Starting heteroaryl substrates. TIPS = triisopropylsilyl.

The reaction of pyrroles **1b–d** with cyclic chiral nitrone (*R*)-**2** is presented in Table 1. In this series, only 1 equiv. of hydrogen chloride was necessary to achieve good conversions of the starting material. Starting from 2-methylpyrrole (**1b**), corresponding cyclic hydroxylamine **3b** was isolated in 55% yield as a unique regioisomer (Table 1, Entry 1). With kryptopyrrole (**1c**), a mixture containing expected **3c** together with corresponding ketimine **7** (see Table 4) was obtained (Table 1, Entry 2). Our attempts to separate the two compounds were unsuccessful. Owing to the lower reactivity of the C-3 position of the pyrrole ring, an increase in the reaction temperature was suitable to obtain **3d** in 86% yield starting from pyrrole **1d** (Table 1, Entries 3 and 4). Hydroxylamine **3e** was also obtained by using the previously described conditions.[14] As it was initially observed with **3a**, products **3b–e** were all obtained as single diastereoisomers.

In the indole series, the reaction of **1f** with nitrone (*R*)-**2** led to corresponding hydroxylamine **3f** in 79% yield (Table 2, Entry 1). Starting from 5-fluoroindole (**1g**), product **3g** was isolated in moderate yield, even after a longer reaction time (Table 2, Entry 2). In this case, the best result was then obtained if the reaction temperature was raised to –20 °C (Table 2, Entry 3). At higher temperatures, corresponding ketimine **7** (see Table 4) was formed in large amounts (Table 2, Entry 4). Again, excellent levels of diastereoselectivity were observed in all cases.

Furan is known to be less nucleophilic than pyrrole.[17] It has also been shown that 2-methylfuran (**1h**) is 1000 times more reactive than furan in trifluoroacetylation reactions.[18] We therefore considered **1h** as a suitable model. At 0 °C, the conversion was low and desired product **3h** was detected only in trace amounts (Table 3, Entry 1). By successively increasing the reaction temperature and the relative amount of reactant **1h**, **3h** was isolated in much better yields (Table 3, Entries 2–4). The best result was finally obtained if 5 equiv. of hydrogen chloride was used (Table 3, Entry 5); the expected product was formed in 73% yield as a unique diastereoisomer.

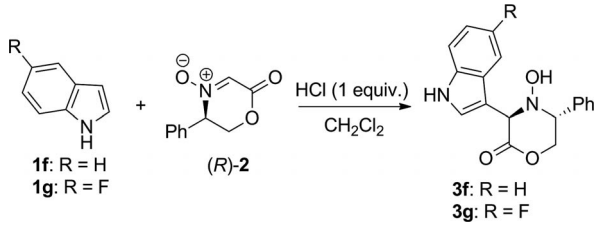
Table 1. Preparation of pyrrolyl hydroxylamines **3b–e**.



Entry	Pyrrole	Product	Conditions	Yield [%]	*dr*[a]
1	**1b**[b]	*rac*-**3b**	–78 to –60 °C, 1 h	55	≥98:2
2	**1c**[b]	*rac*-**3c**	–78 to –60 °C, 1 h	64 (1:1)[c]	≥98:2
3	**1d**	**3d**	–78 to –40 °C, 3 h	59	≥98:2
4	**1d**	**3d**	–20 to 0 °C, 3 h	86	≥98:2
5	**1e**	**3e**	see ref.[14]	–[d]	≥98:2

[a] Diastereomeric ratio of cyclic hydroxylamines **3b–e** was determined by ^{1}H NMR spectroscopy. [b] The reaction was performed by starting from racemic nitrone *rac*-**2**. [c] The **3c/7c** ratio (for the structure, see Table 4), as determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy, is given in parentheses. [d] The yield of the isolated product after two steps is given in Table 4.

Table 2. Preparation of indolyl hydroxylamines **3f** and **3g**.

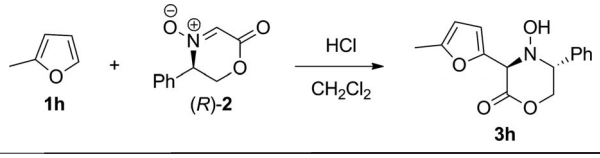


Entry	Indole	Product	Conditions	Yield [%]	*dr*[a]
1	**1f**	**3f**	–78 to –40 °C, 3 h	79	≥98:2
2	**1g**	**3g**	–78 to –40 °C, 6 h	49	≥98:2
3	**1g**	**3g**	–40 to –20 °C, 4 h	64	≥98:2
4	**1g**	**3g**	–20 to 0 °C, 4 h	49[b]	≥98:2

[a] Diastereomeric ratio was determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy. [b] Ketimine **7g** (for the structure, see Table 4) was concomitantly isolated in 26% yield.

With hydroxylamines **3a–h** in hand, we next explored the oxidative sequence for the preparation of the corresponding hydroxyamino esters. As a prerequisite to the subsequent oxidation with lead tetraacetate, it was necessary to perform the transesterification step to convert cyclic hydroxylamines **3** into open-chain hydroxylamines **4**. Upon treatment of ra-

Table 3. Preparation of furyl hydroxylamine **3h**.

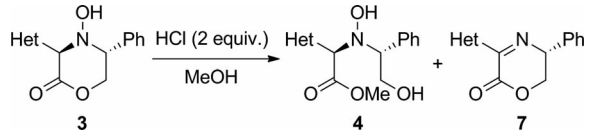


Entry	**1h** [equiv.]	HCl [equiv.]	Conditions	Yield [%]	*dr*[a]
1	1	1	0 °C, 12 h	trace	n.d.
2	1	1	r.t., 72 h	23	≥98:2
3	5	1	r.t., 36 h	28	≥98:2
4	10	1	r.t., 24 h	54	≥98:2
5	10	5	r.t., 10 h	73	≥98:2

[a] Diastereomeric ratio was determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy; n.d. = not determined.

cemic **3b** and **3c** under acidic conditions in methanol at –20 °C, the formation of expected hydroxylamines **4b** and **4c** was not observed, whereas the formation of cyclic ketimines **7b** and **7c** was predominant (Table 4, Entries 1 and 2). The **3c**/**7c** ratio (for the structure, see Table 4) was determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy. Other attempts to convert **3b** and **3c** were performed at –40 °C or by using trifluoroacetic acid as the acidic source, but these reactions gave lower conversion ratios together with the formation of undesired ketimines **7b** and **7c**. However, under the initial conditions, open-chain hydroxylamines **4d**–**h** were obtained in good yields (Table 4, Entries 3–7). Each hydroxylamine **4** was obtained as a single diastereoisomer.

Table 4. Preparation of open-chain hydroxylamines **4**.

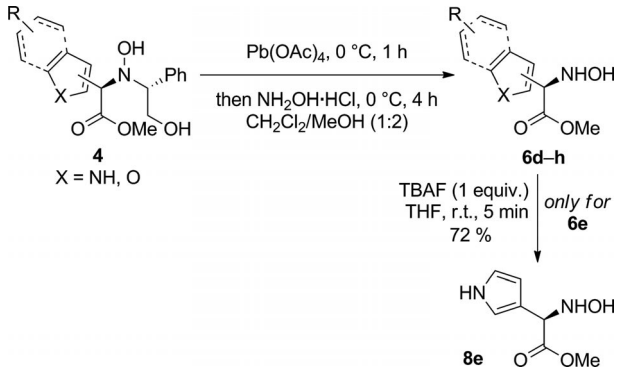


Entry	Hydroxylamine	Product	Conditions	Yield [%]
1	**3b**[a]	**7b**[a]	–20 °C, 12 h	n.d.[b]
2	**3c**[a]	**7c**[a]	–20 °C, 24 h	n.d.[b]
3	**3d**	**4d**	–20 °C, 36 h	51
4	**3e**	**4e**	see ref.[9c,14]	66[c]
5	**3f**	**4f**	–20 °C, 12 h	92
6	**3g**	**4g**	–20 °C, 24 h	78
7	**3h**	**4h**	–20 °C, 24 h	77

[a] Racemic compounds. [b] n.d. = not determined. [c] Yield of isolated product starting from **1e**.

In the next step, hydroxyamino esters **6d**–**h** were obtained through a one-pot sequence consisting in a regioselective oxidation followed by hydroxyaminolysis (Table 5). Under these conditions, **6d**–**h** were obtained in good yield. In the case of the *N*-(triisopropylsilyl)pyrrole derivative, hydroxylamine **6e** was converted into **8e** by cleavage of the TIPS group by using tetra-*n*-butylammonium fluoride (TBAF).

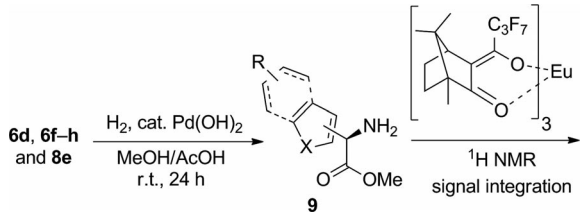
Table 5. Preparation of heteroaryl α-(hydroxyamino) esters **6d**–**h** and **8e**.



Entry	Hydroxylamine	Product	Yield [%]	*ee*[a] [%]
1	**4d**	**6d**	62	90
2	**4e**	**8e**	61[b]	90
3	**4f**	**6f**	85	80
4	**4g**	**6g**	73	76
5	**4h**	**6h**	78	≥98

[a] Determined by integration of the ^{1}H NMR signals by mixing chiral amino ester **9** in the presence of Eu(hfc)$_3$; hfc = 3-(heptafluoropropylhydroxymethylene)-(+)-camphorate. [b] Yield of isolated product over two steps.

All attempts to determine the enantiomeric excess values of final α-(hydroxyamino) esters **6d**–**h** either by HPLC techniques or by ^{1}H NMR spectroscopy in the presence of chiral europium(III) complexes failed. To overcome this problem, the hydroxylamines were reduced into amines in the presence of hydrogen by using Pearlman catalyst, and the *ee* values of the obtained α-amino esters were then measured by ^{1}H NMR spectroscopy in the presence of a chiral europium(III) salt (Scheme 2). As shown in Table 5, the observed enantiomeric excess values were superior to 76%, which is unprecedented for heteroaryl hydroxyamino esters. In the case of the 2-furyl core, final compound **6h** was obtained as a single enantiomer (Table 5, Entry 6).



Scheme 2. Derivatization method for the determination of the enantiomeric excess values of **6d**, **6f**–**h**, and **8e**.

Conclusions

Concise access to optically active α-(hydroxyamino) esters was achieved through the highly diastereoselective addition of heteroaromatics to chiral cyclic nitrone (*R*)-**2**. A subsequent three-step sequence afforded the final products in good overall yields with good to excellent enantiomeric

excess values. The obtained α-(hydroxyamino) esters are key intermediates for the synthesis of peptide sequences containing nonracemic hydroxamate fragments.

Experimental Section

General Procedure for the Preparation of Open-Chain Hydroxylamines 4: To a stirred solution of cyclic hydroxylamine **3** (1 equiv.) in MeOH (0.2–0.4 M) at –40 °C was added HCl (2 N in Et_2O, 2 equiv.). The mixture was warmed at –20 °C and stirred for the appropriate time. The reaction was stopped by the addition of a saturated aqueous solution of $NaHCO_3$ to pH = 8–9. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Obtained hydroxylamine **4** was purified by flash chromatography on silica gel.

General Procedure for the Preparation of α-(Hydroxyamino) Esters 6 and 8e: To a stirred solution of hydroxylamine **4** (1 equiv.) in a mixture of MeOH/CH_2Cl_2 (2:1) at 0 °C was added $Pb(OAc)_4$ (1 equiv.). The mixture was stirred for 1 h, and then $NH_2OH{\cdot}HCl$ (5 equiv.) was added. The resulting mixture was stirred for an additional 4 h. The mixture was then treated with a saturated aqueous solution of $NaHCO_3$ until pH = 8–9. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Obtained α-(hydroxyamino) ester **6** was purified by flash chromatography on silica gel. Unprotected **8e** was obtained by reaction of **4e** with TBAF in anhydrous THF at room temperature for 5 min.

Supporting Information (see footnote on the first page of this article): Typical experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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