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A stereoselective method for the synthesis of enantiopure 3-substituted 4-hydroxyproline derivatives via 1,3-dipolar cycloadditions

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ABSTRACT

The stereoselective 1,3-dipolar cycloaddition between (*Z*)-1,4-dichloro-2-butene and a menthone-derived nitrone led to the corresponding isoxazolidine. Regioselective azidation of a single chlorine atom followed by another Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) induced enantiopure 1,2,3-triazolyl-functionalized isoxazolidines. The subsequent acidic cleavage of the menthone chiral auxiliary and reductive cleavage of the isoxazolidine N–O bond triggered an intramolecular cyclization through the displacement of the second chlorine. This rapid and stereoselective synthetic strategy provided reliable access to a series of enantiopure 3-substituted 4-hydroxyproline derivatives.

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1. Introduction

Hydroxy-L-proline (HP) represents an excellent molecular scaffold for the synthesis of diverse multifunctionalized unnatural amino acids. Such pyrrolidines are challenging targets from a synthetic point of view and have a high potential as biologically active molecules [1]. The introduction of a hydroxyl group at the 3- or 4-position of L-proline could lead to helical oligopeptides displaying on their outer surface the hydroxyl functionality available for further potential conjugation [2]. The present study reports on the stereoselective synthesis of 3-substituted 4-hydroxyproline derivatives via 1,3-dipolar cycloadditions. The obtained scaffolds, therefore, present the hydroxyl group at the 4-position, and a 1,2,3-triazole connected to

the pyrrolidine scaffold through a carbon–carbon bond, at the 3-position.

Menthone-derived nitrones incorporating a glycine equivalent [3] have now demonstrated the potential of 1,3-dipolar cycloadditions with alkenes to create in a single step three contiguous stereogenic centers with strict stereocontrol [4–9]. Various alkenes have been used for the synthesis of diastereoisomers of 4-hydroxyisoleucine [5]. This is a molecule found in fenugreek (*Trigonella foenum-graecum*), a plant traditionally used as an antidiabetic remedy thanks to its insulinotropic properties. An efficient synthesis of (α S,3R,4S)-3-glycinyl-4-hydroxypyrrolidine and 3-substituted 4-hydroxyproline derivatives was also reported with a total control of the stereochemistry (Fig. 1) [6,7]. This strategy is based on a cascade of cycloaddition–cyclization using (*E*)- or (*Z*)-1,4-dichlorobut-2-ene and chiral nitrones as glycine equivalents [6,7]. Another approach in which the nitrone cycloaddition is

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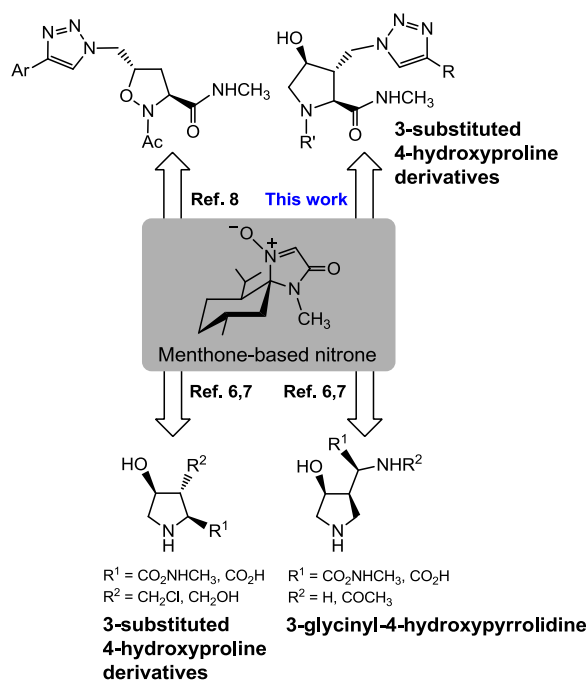


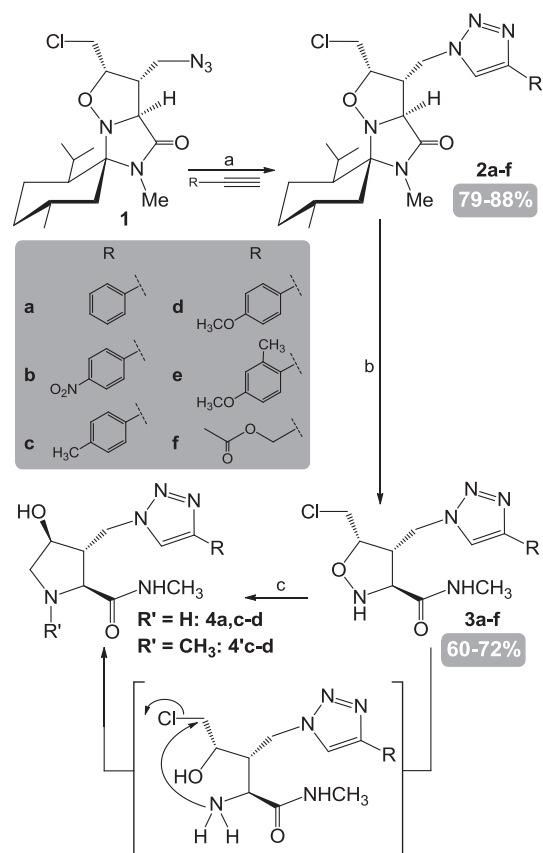
Fig. 1. Selected scaffolds obtained from a common menthone-based nitronium precursor.

followed by a Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) provides rapid access to enantiopure 1,2,3-triazolyloxazolidine derivatives [8]. A recent strategy towards cycloalkylglycines has been demonstrated [9].

The general strategy towards unnatural amino acids originating from menthone-based nitrones as chiral auxiliaries for a glycine derivative can now be applied to the stereoselective synthesis of unprecedented 4-hydroxy-3-substituted proline derivatives in only 6 steps at a high overall yield (Fig. 1). The synthesis proceeds through 1,3-dipolar cycloaddition of the menthone-based nitronium and (*Z*)-1,4-dichloro-2-butene, followed by a regioselective azidation of a chlorine atom and the subsequent installation of a 1,2,3-triazole moiety by microwave-assisted CuAAC. Hydrolytic cleavage of the menthone chiral auxiliary followed by catalytic reduction of the N–O bond led to an amine intermediate that readily cyclized intramolecularly through nucleophilic displacement of the remaining chlorine atom [6,7].

2. Results and discussion

The synthesis of the mono-azido-mono-chlorinated scaffold **1** [6] has been reported. Discussion on the regioselectivity of mono-azidation is provided [6,7]. Copper-catalyzed 1,3-dipolar cycloaddition under microwave irradiation of azide **1** with various functionalized alkynes gave the corresponding 1,2,3-triazoly-1-oxazolidines **2a–f** with high yields (Scheme 1). Acidic cleavage of the chiral auxiliary in **2a–f** under the action of a mixture of acetic acid, acetic anhydride and a catalytic amount of sulfuric acid brought about methylamides



Scheme 1. Synthesis of enantiopure 3-substituted 4-hydroxyproline derivatives. Reagents and conditions: (a) *i*Pr₂NEt, CuI, μ W, DMF, 110 °C, 15 min; (b) AcOH, Ac₂O, cat. H₂SO₄, 50 °C, 6.5 h; (c) H₂ (1 atm), Pd(OH)₂, MeOH, rt, 4 days.

3a–d,f with good yields. In the case of isoxazolidine **2e**, the same reaction was attempted but without success. The structure of isoxazolidine **3a** was unambiguously determined by a single crystal X-ray diffraction analysis [10] (Fig. 2). It provided reliable data for the structural characterization of this series of intermediates.

4-Chloromethyl isoxazolidines **3a–f** can be readily converted to the corresponding pyrrolidines **4** upon reduction of the N–O bond and subsequent nucleophilic

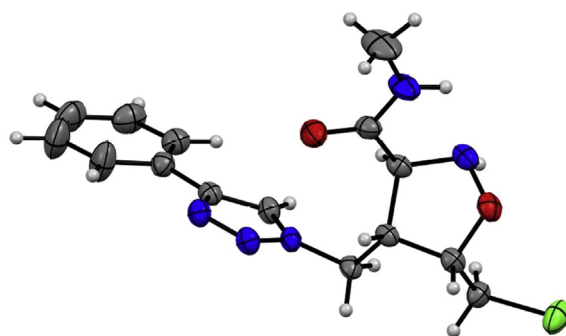


Fig. 2. ORTEP representation of the crystal structure of **3a**.

displacement of the chlorine atom by the generated amine functionality [6]. Indeed, reductive cleavage under hydrogenolysis conditions of the N–O bond of the 4-chloromethyl isoxazolidine **3a** led to the enantiopure methylamide **4a** in an almost quantitative yield. Meanwhile, catalytic hydrogenolysis applied to compounds **3c–d** led to a separable mixture of **4c–d** (27 and 15%) and **4'c–d** (70 and 84%). In the case of compounds **3b,f**, the reaction led to a complex mixture of inseparable products. For compound **3b**, the opening of the N–O bond by catalytic hydrogenation (H_2 , Pd/C) induced an inseparable mixture of products. The NO_2 group was most probably reduced to NH_2 and further unexpected reactivities may be observed. In the case of compound **3f**, the acetate might be cleaved by intra- or intermolecular reaction with the generated amine leading to an inseparable mixture of products. Two other conditions for the cleavage of the N–O bond were then applied [$Mo(CO)_6$, CH_3CN-H_2O [11]; Zn, AcOH [3b]] for these compounds but without success.

The obtained *N*-methylated products **4'c–d** were reported in the *N*-alkylations of amines carried out using different alcohols as the solvent and with 10% Pd/C or 20% Pd(OH)₂/C as the catalyst at room temperature [12].

3. Conclusion

In conclusion, 1,3-dipolar cycloaddition of a menthone-based nitron to (*Z*)-1,4-dichloro-2-butene occurred with the simultaneous creation of three contiguous stereogenic centers to afford a dichlorinated isoxazolidine-based cycloadduct. Regioselective substitution of the chlorine atom by an azide group, followed by another azide–alkyne 1,3-dipolar cycloaddition (CuAAC) induced enantiopure 1,2,3-triazolyl-functionalized isoxazolidines. Acidic cleavage of the chiral auxiliary led directly to the 3-methylamide isoxazolidines. An amino group was then generated by reductive cleavage of the isoxazolidine N–O bond which triggered an intramolecular cyclization. This rapid and stereoselective synthetic strategy provides reliable access to a series of enantiopure 3-substituted 4-hydroxyproline derivatives.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.crci.2016.03.003>.

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- [10] Crystal data for compound **3a**: $C_{15}H_{18}ClN_5O_2$, $M_r = 335.79 \text{ g}\cdot\text{mol}^{-1}$, monoclinic, $P1\ 21\ 1$, $a = 10.8355$ (2) Å, $b = 10.8865$ (2) Å, $c = 14.5653$ (4) Å, $\alpha = \gamma = 90^\circ$ and $\beta = 106.481$ (2), $D_{\text{calc}} = 1.354 \text{ g}\cdot\text{cm}^{-3}$, $Z = 4$, independent reflections = 5824 ($R_{\text{int}} = 0.038$), R values [$I > 2\sigma(I)$, 5488 reflections]: $R_1 = 0.036$, $wR_2 = 0.076$; $S = 1.00$; CCDC 1046833.
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