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Domino metal-free allene-β-lactam-based access to functionalized pyrroles†

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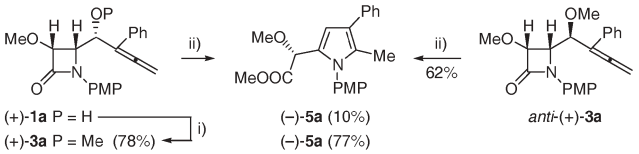
Received (in Cambridge, UK) 26th January 2006, Accepted 25th April 2006
First published as an Advance Article on the web 19th May 2006
DOI: 10.1039/b601238h

Published on 19 May 2006. Downloaded by University of California - Santa Cruz on 30/10/2014 01:57:06.

A novel transition metal-free domino reaction sequence in allene-β-lactams, leading to the biologically relevant pyrrole frame has been developed using a sodium methoxide–methanol system.

Of the various synthetic and naturally occurring heterocyclic structures, pyrrole derivatives are among the most prevalent, because of their remarkable pharmacological activities.[1] Furthermore, pyrroles are useful intermediates in the synthesis of natural products as well as in heterocyclic chemistry,[2] and they are widely used in materials science.[3] Recently, organometallic transformations have been pursued with renewed interest to approach the elusive addition reaction of the N–H bond across allenes.[4] On the other hand, in addition to the key role that β-lactams have played in the fight against pathogenic bacteria, the use of 2-azetidinones as chiral building blocks in organic synthesis is now well established.[5] Although many efforts have been made in these fields, the direct preparation of the pyrrole ring from β-lactams has not been reported yet. Furthermore, the use of the allenamine building block for the synthesis of pyrroles has remained seldom explored.[6] We recently reported that the 2-azetidinone nucleus is the precursor of different types of nitrogen-containing molecules.[7] As a cleaner alternative to the use of metal-containing reagents and catalysts, herein, we present a powerful methodology for the preparation of functionalized pyrroles, which relies on a base-promoted domino reaction in allene-β-lactams.

Precursors for the pyrrole formation, α-allenols **1** and **2**, were made starting from the appropriate 4-oxoazetidine-2-carbaldehyde or azetidine-2,3-dione *via* indium-mediated Barbier-type carbonyl–allenylation reaction in aqueous media using our previously described methodologies.[8] α-Allenols **1** and **2** were protected as the corresponding methyl ethers **3** and **4** by treatment with dimethyl sulfate under phase transfer conditions. During the search for a suitable protocol for the preparation of enantiopure β-allenamines, we detected an unexpected and interesting formation of highly functionalized enantiopure pyrrole derivatives. In an initial experiment, α-allenyl methyl ether (+)-**3a** and sodium methoxide were mixed in methanol at room temperature. To our delight, the

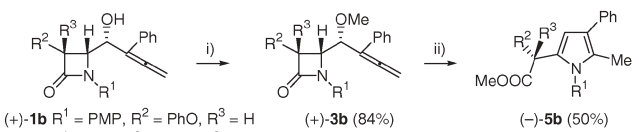


Scheme 1 One-pot synthesis of pyrrole (−)-**5a** through domino β-lactam ring opening–allene cyclization. Reagents and conditions: (i) Me_2SO_4, NaOH, TBAI, DCM–H_2O, RT; (ii) MeONa, MeOH, RT. PMP = 4-$MeOC_6H_4$.

above reaction gave as the only product the 1,2,3,5-tetrasubstituted pyrrole (−)-**5a** in reasonable yield (77%) and total regioselectivity. Compound (−)-**5a** can be considered as a hybrid scaffold as combination of the biological and synthetically relevant pyrrole and α-hydroxy acid cores.[9] The susceptibility of the reaction to stereochemically different β-lactam allenic ethers was examined by exploring the possibility of employing 2-azetidinone-tethered allene *anti*-(+)-**3a**. Gratifyingly, pyrrole (−)-**5a** was obtained in similar selectivity and yield (Scheme 1). When the reaction was performed on unprotected α-allenol (+)-**1a**, the domino sequence provided the desired product (−)-**5a** but in low yield (10%).

Reactions of a variety of β-lactam allenic ethers with sodium methoxide gave the expected functionalized pyrroles in reasonable isolated yields without the need for a transition metal catalyst.[10] No other regioisomers were observed in all cases. Typical results are shown in Scheme 2. Although complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures, some decomposition was observed on sensitive pyrroles **5a–e** during purification by flash chromatography, which may be responsible for the moderate isolated yields.

The influence of the position of the allene moiety at the β-lactam ring for the one-pot synthesis of the pyrrole nucleus, was



Scheme 2 One-pot synthesis of pyrroles **5b–e** through domino ring opening–cyclization reaction of β-lactam allenic ethers **3b–e**. Reagents and conditions: (i) Me_2SO_4, NaOH, TBAI, DCM–H_2O, RT; (ii) MeONa, MeOH, RT. PMP = 4-$MeOC_6H_4$; (+)-**1b**, (+)-**3b**, and (−)-**5b** (R^1 = PMP, R^2 = PhO, R^3 = H); (+)-**1c**, (−)-**3c**, and (−)-**5c** (R^1 = allyl, R^2 = MeO, R^3 = H); (±)-**1d**, (±)-**3d**, and (±)-**5d** (R^1 = PMP, R^2 = Me, R^3 = H); (+)-**1e**, (+)-**3e**, and (−)-**5e** (R^1 = PMP, R^2 = MeO, R^3 = allyl).

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† Electronic supplementary information (ESI) available: Compound characterization data and experimental procedures for all new compounds. See DOI: 10.1039/b601238h

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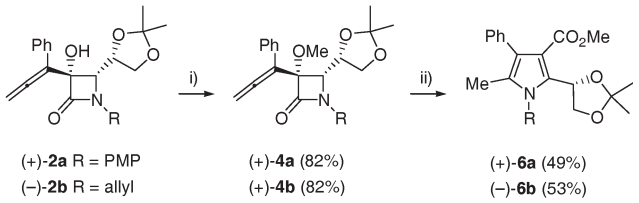


(+)-**2a** R = PMP
(−)-**2b** R = allyl

(+)-**4a** (82%)
(+)-**4b** (82%)

(+)-**6a** (49%)
(−)-**6b** (53%)

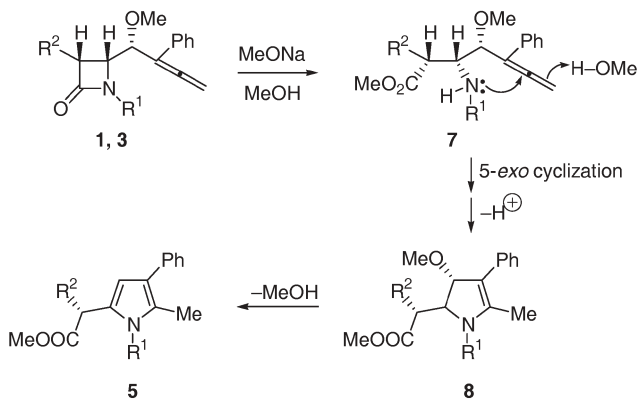
Scheme 3 One-pot synthesis of pyrroles **6a–b** through domino ring opening–cyclization reaction of β-lactam allenic ethers **4a–b**. Reagents and conditions: (i) Me_2SO_4, NaOH, TBAI, DCM–H_2O, RT; (ii) MeONa, MeOH, reflux. PMP = 4-$MeOC_6H_4$.

investigated by stirring protected quaternary α-allenols **2** for 48 h in a mixture of MeONa in MeOH at room temperature. After workup, the starting materials were recovered. Only after heating at reflux temperature did the β-lactam α-allenic ethers **4** react to form the corresponding heterocycles.[10] New pentasubstituted pyrroles **6** were obtained in fair yields by means of our metal-free procedure, without the concomitant formation of any regioisomer (Scheme 3).[11]

From a mechanistic point of view, our domino sequence could be explained through a bond breakage process on the four-membered lactam followed by allene cyclization, with concomitant aromatization. The selective N1–C2 bond cleavage of the β-lactam nucleus in 2-azetidinone-tethered allenes **1**, **3** gave the non-isolable allenic-β-amino esters **7**, which after a totally regioselective cyclization onto the central carbon atom of the neighbouring allene under the reaction conditions followed by aromatization of the pyrrolines **8** yielded the pyrroles **5** (Scheme 4).[12] The pyrrole formation must be driven by relief of the strain associated with the four-membered ring, on forming a more stable five-membered ring.

In conclusion, using a simple reagent we have successfully accomplished an unprecedented domino lactam ring opening–allene cyclization reaction for the construction of the biologically relevant pyrrole frame. Studies concerning the scope and generality of this methodology, as well as mechanistic implications are underway in our laboratory, and further details will be reported in due course.‡

Support for this work by the DGI-MEC (Project BQU2003-07793-C02-01) is gratefully acknowledged. M. C. R. thanks the MEC for a predoctoral grant.



Scheme 4 Possible reaction course for the domino ring opening–allene cyclization sequence.

Notes and references

‡ Representative experimental procedure for the synthesis of pyrroles **5**: Sodium methoxide (0.6 mmol) was added in portions at 0 °C to a solution of the appropriate allene-β-lactam **3** (0.15 mmol) in methanol (3 mL). The reaction was stirred at room temperature under argon atmosphere until complete disappearance of the starting material (TLC) and then water was added (0.5 mL). The methanol was concentrated under reduced pressure, the aqueous residue was extracted with ethyl acetate (5 × 3 mL), the organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Chromatography of the residue on deactivated silica gel eluting with ethyl acetate–hexanes mixtures gave analytically pure compounds **5a–e**.

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10 No loss of enantiomeric purity was evident by the ^{1}H NMR spectra in the presence of a chiral shift reagent of europium(III). Typically, after the addition of the chiral shift reagent the signals for enantiopure pyrroles moved about *ca.* 0.3 ppm downfield. For racemates, after the addition of the chiral shift reagent, the signals for both enantiomers in the

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^{1}H NMR spectra can be differentiated *ca.* 0.4 ppm. Besides, in the ^{1}H NMR spectra of the racemates after the addition of the chiral shift reagent, the hydrogens of the enantiomers not prepared in this work were upfield of the analogous hydrogens of our enantiopure pyrrole derivatives.

11 Another structural feature which is often associated with pronounced physiological activities of pyrroles, is the presence of hydroxymethyl functionalities at the 2-position. Recently, 2-(hydroxymethyl)pyrroles were discovered as a new class of inhibitors of α-chymotrypsin, as well as central analgesics. See: D. C. Martin, A. J. Vernall, B. M. Clark and A. D. Abell, *Org. Biomol. Chem.*, 2003, **1**, 2103; A. D. Abell and B. K. Nabbs, *Bioorg. Med. Chem.*, 2001, **9**, 621; D. Della Bella, A. Carenzi, M. Cibin and N. Gentile, *Eur. Pat. Appl.*, 1992, EP 480458 A2 19920415; *Chem. Abstr.* 1992, **117**, 14434; in addition 2-(hydroxymethyl)pyrroles are versatile intermediates in the synthesis of natural products, especially porphyrins and related pyrrole oligomers. See: A. R. Katritzky and J. Li, *J. Org. Chem.*, 1996, **61**, 1624.

12 One of the referees has suggested that compounds **5** might also arise from a 5-*endo* process, leading either to an intermediate stabilized benzylic anion, or directly to S_N2' displacement of methoxide.

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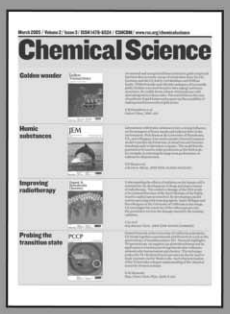

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