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Stereoselective synthesis of highly functionalised tricyclic β-lactams via intramolecular nitrilimine cycloaddition

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Abstract—The novel azeto[2′,1′:1,2]pyrrolo[3,4-*c*]pyrazole skeleton has been obtained in both racemic and enantiopure forms by means of intramolecular cycloaddition of nitrilimines **6**. Fully stereoselective cycloadditions were obtained, giving tricyclic β-lactams **7** as single diastereoisomers with good overall yields.

1. Introduction

Due to their widespread application in the treatment of a number of infective diseases, the relevance of β-lactam derivatives in the field of medicinal chemistry is well documented.[1] As a consequence, several strategies devoted to the synthesis of new β-lactam antibiotics have been developed,[2] giving rise to a large number of compounds featuring enhanced antibacterial activity[3] or better resistance towards β-lactamases.[4] Within this developing picture, the approach to tricyclic β-lactams involving a 1,3-dipolar cycloaddition as the key step has been exploited in recent times.[5] As an example, the intramolecular nitrone-olefin cycloaddition allowed the synthesis of tricyclic β-lactams, which display an astonishing array of latent functionalities.[6] Much less work has been carried out with other types of 1,3-dipoles, namely, nitrilium betaines.[7] In line with our recent reports on the synthesis of tricyclic β-lactams,[8] we herein report a straightforward procedure for preparing racemic and enantiopure azeto[2′,1′:1,2]pyrrolo[3,4-*c*]pyrazole skeletons by exploiting the intramolecular 1,3-dipolar cycloaddition of suitably functionalised nitrilimines.

2. Results and discussion

Our synthetic sequence is depicted in Scheme 1. α,β-Unsaturated imines **1a**[9] and **1b** were readily obtained by reacting glycine methylester or L-alanine methylester, respectively, with cinnamaldehyde. Subsequent [2+2] Staudinger cycloaddition between the C=N double bond of **1** and phenoxyketene generated in situ from phenoxyacetyl chloride gave β-lactams **2**,[10] which, as expected, were cis substituted at the 3- and 4-position of the four-membered ring.[1] In the case of homochiral imine **1b**, however, the corresponding **2b** was obtained as the major isomer (67:33) of a mixture of the two possible diastereoisomeric β-lactams. Chromatographic treatment of the latter mixture gave enantiopure **2b**, which was used further. Acyl hydrazines **4a** and **b** were obtained from **2a** and **b** through ester hydrolysis, carboxyl activation with oxalyl chloride and subsequent treatment with phenylhydrazine. Hydrazonoyl chlorides **5a** and **b** were synthesised from the corresponding acyl hydrazines via treatment with triphenylphosphine and carbon tetrachloride, according to the method originally proposed by Wolkoff.[11] The in situ generation of labile intermediates **6a** and **b** was accomplished by heating at 50 °C the corresponding hydrazonoyl chlorides **5** in dry dioxane in the presence of silver carbonate as the basic agent.[12] After 24 h, racemic cycloadduct **7a** and enantiopure **7b** were obtained in 65% and 76% yield, respectively.

Formulae **7a** and **b** rely upon analytical and spectral data.[13] In particular, the scalar couplings between the two hydrogens at the 3- and 4-position of the β-lactam ring (H_A and H_B, $J = 4.0$ Hz) reflect their cis arrangement,[14] while the value of 9.1–9.3 Hz, which refers to the two hydrogens in the 4- and 5-position of the 4,5-dihydropyrazole ring (H_C, H_D) agrees with their trans relationship.[15] These

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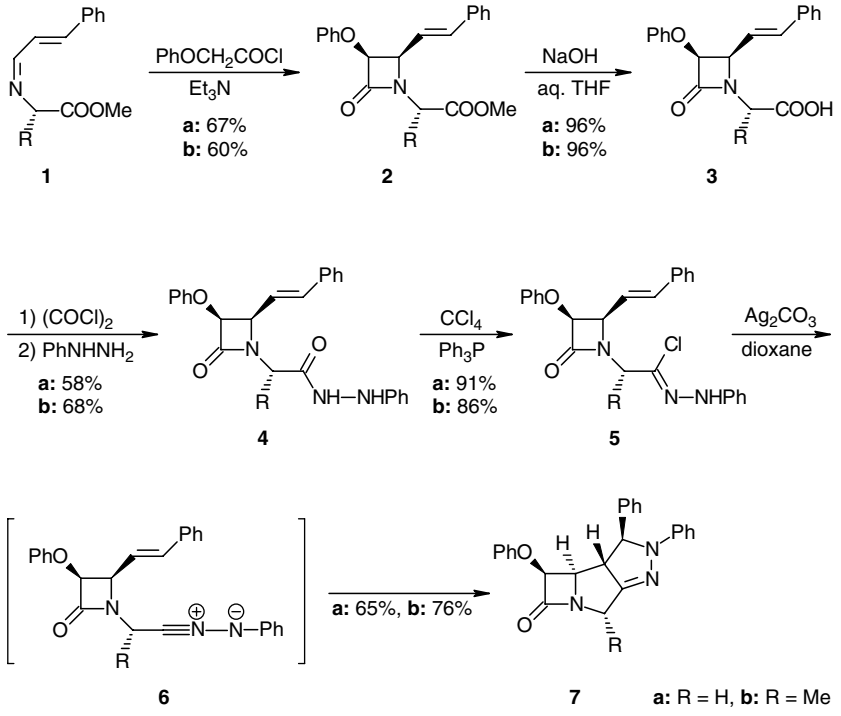

Scheme 1.

findings are consistent with the following statements: (i) β-lactam ring stereochemistry is retained through dipolar cycloaddition, and (ii) 4,5-dihydropyrazole ring stereochemistry is dictated from the stereoselectivity typical of concerted dipolar cycloadditions.

From these considerations, it follows that the relative configurations of the two stereocentres placed on the tetrahydropyrrole ring of both racemic **7a** and enantiopure **7b** (H_B, H_C) can be safely deduced from the observed NOE enhancements between H_B and H_D (Fig. 1).[16] Furthermore, the absolute configurations of the newly formed stereocentres of enantiopure (3*S*,5*S*,5a*R*,6a*S*,6*S*)-**7b** were unambiguously determined from the NOE enhancements between H_B and the average position of H_E. It is apparent that these NOE effects can only be operative in the case of the stereochemical arrangement depicted. In order to further substantiate these NOE effects, the distances H_B–H_D and H_B–H_E were calculated with the AM 1[17] semi-empirical method. Values of 2.25 Å for **7a** and 2.27 Å (H_B–H_D) and 2.89 Å (H_B–H_E) for **7b**[18] were found, thus justifying the observed mutual NOE enhancements. As far as cycloaddition diastereoselectivity is concerned, we were pleased to find that both **7a** and **7b** were obtained as single diastereoisomers. This favourable stereochemical outcome may be accounted for by considering the steric crowding of the *Si* face of the ethylenic dipolarophile.

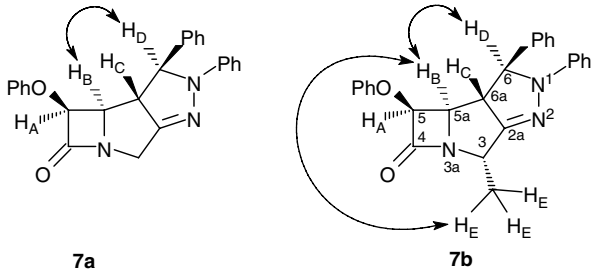

Figure 1.

3. Conclusion

In conclusion, we demonstrated the feasibility of intramolecular cycloaddition between nitrilimines and the ethylenic dipolarophile, which are tethered by the β-lactam ring. Highly functionalised tricyclic β-lactams were obtained with good overall yields and complete diastereoselectivity.

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12. A solution of **5** (1.3 mmol) in dry dioxane (20 mL) was treated with silver carbonate (1.76 g, 6.5 mmol) and warmed to 50 °C in the dark under a nitrogen atmosphere for 24 h. The residue was filtered off, the solvent evaporated under reduced pressure and the residue was chromatographed on a silica gel column with ethyl acetate–hexane 3:7 to give **7**.
13. Selected data for compound **7a**: ^{1}H NMR ($CDCl_3$) δ 3.83 (2H, m), 4.12 (1H, dd, *J* 8.0, 4.0), 4.42 (1H, dd, *J* 9.3, 8.0), 4.93 (1H, d, *J* 9.3), 5.51 (1H, d, *J* 4.0), 6.7–7.3 (15H, m); ^{13}C NMR ($CDCl_3$) δ 43.0 (t), 60.3 (d), 61.0 (d), 71.8 (d), 78.8 (d), 114.2–129.7, 140.3 (s), 146.4 (s), 156.3 (s), 156.8 (s), 173.5 (s). Compound **7b**: ^{1}H NMR ($CDCl_3$) δ 1.55 (3H, d, *J* 6.6), 3.86 (1H, q, *J* 6.6), 4.11 (1H, dd, *J* 8.0, 4.0), 4.42 (1H, dd, *J* 9.1, 8.0), 4.94 (1H, d, *J* 9.1), 5.47 (1H, d, *J* 4.0), 6.8–7.3 (15H, m); ^{13}C NMR ($CDCl_3$) δ 18.0 (q), 50.5 (d), 59.7 (d), 60.6 (d), 73.2 (d), 78.4 (d), 114.1–129.7, 140.5 (s), 146.5 (s), 156.3 (s), 160.4 (s), 173.2 (s).
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16. NOE experiments were performed on a Bruker AMX 300 instrument by setting the following parameters: relaxation delay (d1) 2 s, irradiation power (dl2) 74 dB and total irradiation time (for each signal) 1.8 s.
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