Pergamon

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Tetrahedron Letters 44 (2003) 1425–1427

TETRAHEDRON LETTERS

Nitrilimine cycloaddition to 4-(pyrazol-5-yl)carbonyl-2-azetidinone and 4-(pyrazol-4-yl)carbonyl-2-azetidinone

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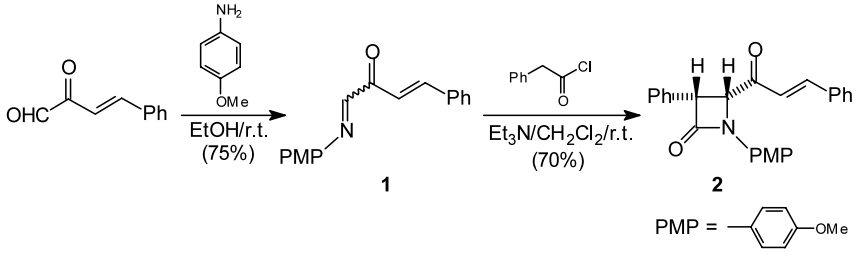
Received 18 November 2002; revised 25 November 2002; accepted 18 December 2002

Abstract—The higly stereoselective nitrilimine cycloaddition onto the novel 3(*R**)-phenyl-4(*S**)-cinnamoyl-2-azetidinone **2** gave 4-(4,5-dihydropyrazol-5-yl)carbonyl-2-azetidinone **5** as the major product and 4-(4,5-dihydropyrazol-4-yl)carbonyl-2-azetidinone **6** as the minor one. Ceric ammonium nitrate (CAN) oxidation of the cycloadducts gave the title compounds with good overall yield.

Due to their antibiotic or β-lactamase inhibitor activity, 2-azetidinone-based heterocycles represent a very attractive target of contemporary organic synthesis.[1] Furthermore, the pyrazole and 4,5-dihydropyrazole rings are found in several compounds which display biological activity as antiinflammatory[2] and anticoagulating[3] factors. The present letter is concerned with the first synthesis of 4-(pyrazol-5-yl)carbonyl-2-azetidinone and 4-(pyrazol-4-yl)carbonyl-2-azetidinone, which brings together the above-mentioned heterocyclic fragments, by means of a nitrilimine 1,3-dipolar cycloaddition.

First, we devised the novel 3(*R**)-phenyl-4(*S**)-cinnamoyl-2-azetidinone **2**[4] as a suitable starting building block, which was readily obtained in good overall yield from cinnamoylcarboxaldehyde.[5] The two steps involved were: (i) condensation of the latter with 4-methoxy aniline and (ii) Staudinger [2+2] cycloaddition between imine **1** and phenylketene, which was generated in situ by base treatment of phenylacetyl chloride (Scheme 1).

Next, hydrazonoyl chloride **3**[6] was treated with an equimolecular amount of silver acetate in dry dioxane in the presence of **2**. Besides the recovery of unreacted **2** (15%), 1,3-dipolar cycloaddition of the labile nitrilimine intermediate **4** gave regioisomeric (4*R**,5′*S**)-**5** and (4*R**,4′*R**)-**6** in the ratio **5**:**6** = 80:20 with a 70% overall yield (Scheme 2). Product separation was achieved on silica gel column chromatography with *t*BuOMe–light petroleum 55:45 as eluent, while analytical and spectroscopic data of the cycloadducts are in full agreement with the formulae depicted.[7] The regioselectivity of the cycloaddition is not surprising and matches that usually observed in the reaction



Scheme 1.

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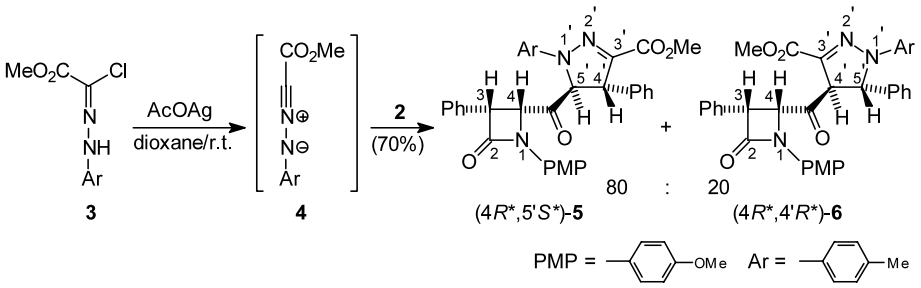


Scheme 2.

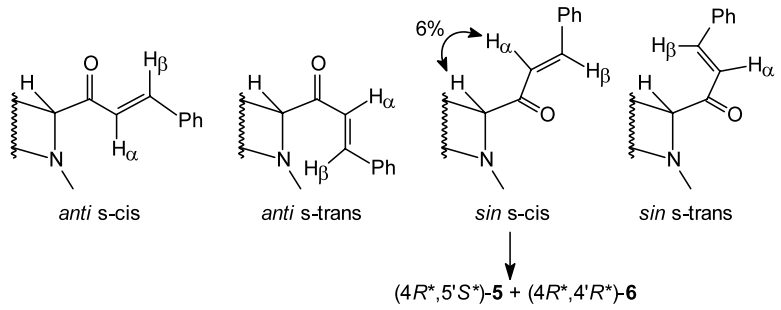


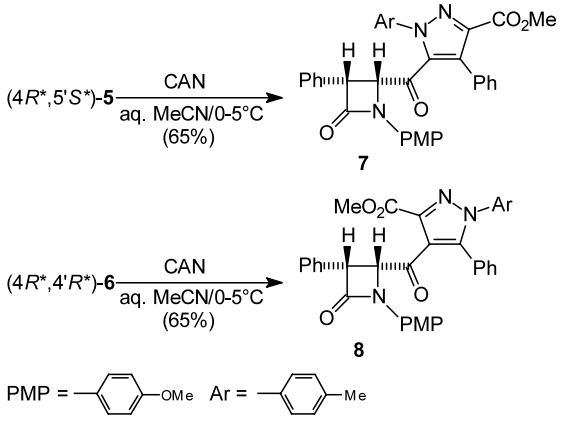
Figure 1.

between nitrilimines and α,β-unsaturated carbonyl derivatives.[8] On the other hand, both major product (4*R**,5′*S**)-**5** and minor product (4*R**,4′*R**)-**6** were detected as single stereoisomers, the cycloaddition being therefore fully stereoselective. Inspection of Dreiding stereomodels of **2** showed that (i) the phenyl ring in the 3-position of the 2-azetidinone fragment effectively hinders one of the two diastereofaces of the C=C dipolarophile, and (ii) due to unavoidable steric crowding, a free interchange between the four possible conformations of the cinnamoyl moiety in the 4-position is precluded. A pictorial representation of these conformations is given in Figure 1, while AM1[9] computed distances H–H_α and H–H_β are summarised in Table 1. In the light of the observed NOE enhancement (6%) of H_α when irradiating H, it follows that the *syn s-cis* arrangement is the only reasonable candidate describing the ground state conformation of **2**, thus allowing the stereoselective formation of (4*R**,5′*S**)-**5** and (4*R**,4′*R**)-**6**. As a further step of our work, we submitted the latter cycloadducts to oxidation with ceric ammonium nitrate (CAN), and obtained 4-(pyrazol-5-yl)carbonyl-2-azetidinone **7** and 4-(pyrazol-4-yl)carbonyl-2-azetidinone **8**, respectively (Scheme 3).[10] These compounds gave crystals suitable for X-ray diffractometric analyses (Fig. 2),[11] thus demonstrating unambiguously the regiochemical outcome of the nitrilimine cycloaddition. In conclusion, the present study provides the first insight into the regio- and stereoselectivity involved in the nitrilimine cycloaddition to higly-functionalised 2-azetidinones. Further developments are in progress.

Table 1. AM1-calculated distances between H–H_α and H–H_β[a]

Entry	*anti s-cis*	*anti s-trans*	*syn s-cis*	*syn s-trans*
H–H_α	3.69	4.46	**2.48**	3.91
H–H_β	4.72	3.71	4.60	**2.28**

[a] Distance in Å.



Scheme 3.

Acknowledgements

We would like to thank MURST and CNR for financial support. We would also like to gratefully thank student Dr. Paolo Anesa.

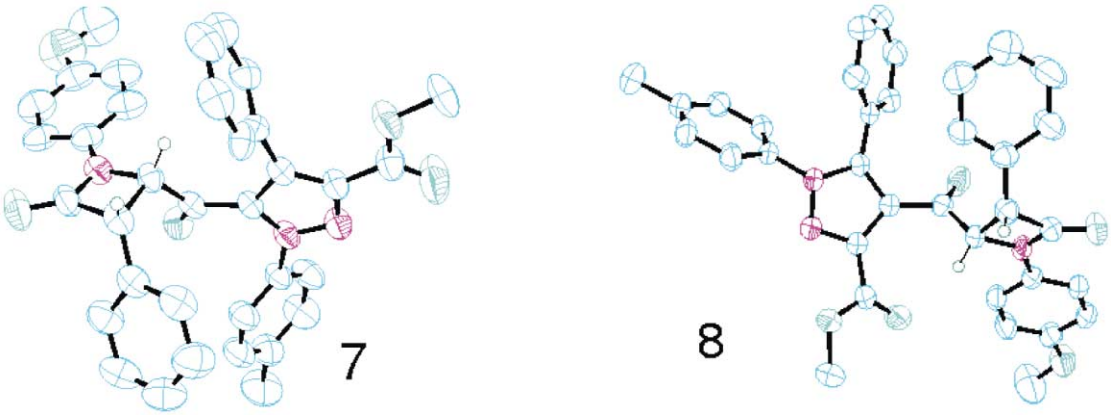


Figure 2.

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4. Selected data for **2**: mp 202°C (from ethanol); IR (Nujol): ν_{max} 1740, 1690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.72 (3H, s), 4.93 (1H, d, $J=6.5$), 5.07 (1H, d, $J=6.5$), 6.46 (1H, d, $J=16.0$), 6.8–7.2 (15 H, m).
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7. Selected data for (4*R**,5′*S**)-**5** and (4*R**,4′*R**)-**6**. (4*R**,5′*S**)-**5**: mp 200°C (from iPr_2O); IR (Nujol): ν_{max} 1745, 1730, 1685 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.14 (3H, s, $C\underline{H}_3C_6H_4$-), 3.67 (1H, d, $J=4.2$, C'_4-$\underline{H}$), 3.71 (3H, s, $C\underline{H}_3OC_6H_4$-), 3.90 (3H, s, $C\underline{H}_3OOC$-), 4.89 (1H, d, $J=6.6$, C_3-$\underline{H}$), 5.32 (1H, d, $J=4.2$, C'_5-$\underline{H}$), 5.80 (1H, d, $J=6.6$, C_4-$\underline{H}$), 6.8–7.5 (18 H, m, aromatics). (4*R**,4′*R**)-**6**: mp 207°C (from iPr_2O); IR (Nujol): ν_{max} 1760, 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.35 (3H, s, $C\underline{H}_3C_6H_4$-), 3.70 (3H, s, $C\underline{H}_3OC_6H_4$-), 3.77 (3H, s, $C\underline{H}_3OOC$-), 4.10 (1H, d, $J=3.2$, C'_4-$\underline{H}$), 4.57 (1H, d, $J=3.2$, C'_5-$\underline{H}$), 4.79 (1H, d, $J=6.3$, C_3-$\underline{H}$), 5.07 (1H, d, $J=6.3$, C_4-$\underline{H}$), 6.7–7.4 (18 H, m, aromatics).
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9. As implemented in the HyperChem Professional 6.03 version, 2000.
10. Selected data for **7** and **8**. **7**: mp 183°C (from iPr_2O); IR (Nujol): ν_{max} 1750, 1730, 1685 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.32 (3H, s, $C\underline{H}_3C_6H_4$-), 3.74 (3H, s, $C\underline{H}_3OC_6H_4$-), 3.79 (3H, s, $C\underline{H}_3OOC$-), 4.42 (1H, d, $J=6.5$, C_3-$\underline{H}$), 4.78 (1H, d, $J=6.5$, C_4-$\underline{H}$), 6.3–7.7 (18 H, m, aromatics). **8**: mp 209°C (from iPr_2O); IR (Nujol): ν_{max} 1740, 1715, 1685 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.28 (3H, s, $C\underline{H}_3C_6H_4$-), 3.77 (3H, s, $C\underline{H}_3OC_6H_4$-), 4.08 (3H, s, $C\underline{H}_3OOC$-), 4.82 (1H, d, $J=6.6$, C_3-$\underline{H}$), 6.07 (1H, d, $J=6.6$, C_4-$\underline{H}$), 6.9–7.5 (18 H, m, aromatics).
11. Crystallographic data (excluding structure factors) for structures **7** and **8** have been deposited with the Cambridge Crystallographic data Centre as supplementary publication numbers CCDC 197536 and CCDC 197535, respectively.