Pergamon

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Tetrahedron Letters 44 (2003) 5053–5055

TETRAHEDRON LETTERS

A novel nucleophilic attack to *N*-enoyl oxazolidinethiones

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Received 28 March 2003; revised 29 April 2003; accepted 7 May 2003

Abstract—The oxazolidinethione synthon can act as a chiral auxiliary and nucleophile (S^-) carrier molecule simultaneously. Surprisingly, the thiolate attacks *N*-enoyl oxazolidinethiones producing a new heterocycle, as established by X-ray analysis.

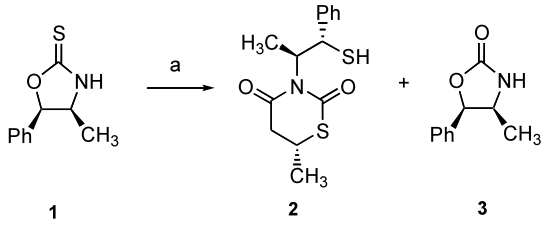
The oxazolidinethione structure has been widely used as a chiral auxiliary in different types of synthetic transformations. The asymmetric Diels–Alder reaction of its corresponding *N*-enoyl[1] and aldol reaction of *N*-acyl derivatives with aldehydes,[2,3] are important applications of oxazolidinethiones in the total synthesis of biologically important natural products.[4]

Currently the obtention of *N*-acyl or *N*-enoyl oxazolidinethiones is realized by different methods, using acyl chlorides and different bases like *n*-butyl lithium,[2] pyridine,[5] triethylamine[6] and sodium hydride[2,7] but in no methods have the characteristics that the base requires to react with the amidic proton been described.

On the other hand cleavage of oxazolidinethiones derivatives is easier than in *N*-acyl or *N*-enoyl oxazolidinones. Furthermore it has been described recently that *N*-enoyl oxazolidinethiones show a novel intramolecular sulfur atom transfer reaction to α,β-unsaturated systems promoted by Lewis acid to yield β-mercapto carboxylic acid derivatives.[8,9] This reaction was undetected in the case of oxazolidinones derivatives.

In this paper we describe an interesting side reaction observed during the attempted attachment of thione-type auxiliaries to *trans*-crotonyl chloride, where the oxazolidinethiones act as chiral auxiliary and nucleophile thiolate carrier molecules, simultaneously. This was probed in the context of the illustrated reaction with chiral auxiliary **1**.

Chiral auxiliary **1** was prepared from the commercially available (1*R*,2*S*) norephedrine under the reaction conditions described previously,[9] followed by deprotonation with NaH and acylation with 0.5 equiv. of *trans*-crotonyl chloride to afford **2** as a white crystalline solid[10] in 65% yield, mp 133–135°C, $[\alpha]_D^{25} = +159.4$, $c = 0.96$ $CHCl_3$, and the corresponding oxazolidinone **3** (Scheme 1).



1 2 3

Scheme 1. *Reagents and conditions*: (a) NaH (1.1 equiv.), THF, 0°C, 45 min, *trans*-crotonyl chloride (0.5 equiv.), 0°C, 1 h.

The new product **2** was prepared by in situ formation of the corresponding *N*-enoyl derivative and subsequent thiolate addition (via S_N2) of **1** at the C-5 position of the *N*-enoyl oxazolidinethione, followed by a cyclization assisted by the known intramolecular rearrangement,[8,9] and hydrolysis (Scheme 2).

The absolute configurations at the newly formed stereogenic centers (C-6, C-8) are *R* and *S*, respectively, as established by X-ray analysis[11] of compound **2**, derived from norephedrine (Fig. 1). The X-ray structure of **2** shows the expected six-membered ring for the heterocycle, in which all atoms are nearly planar except for C-6. It should be mentioned that few X-ray characteriza-

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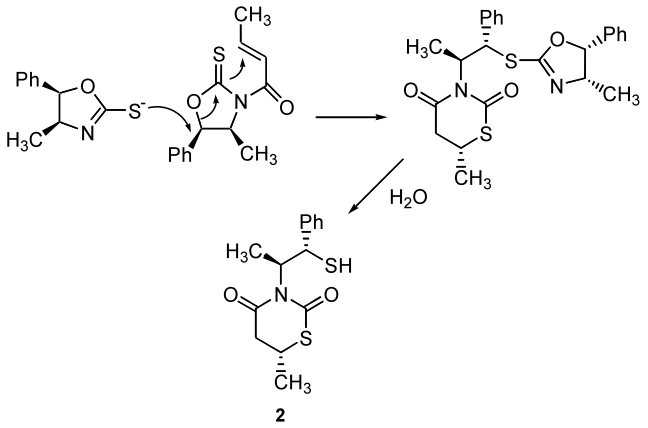
doi:10.1016/S0040-4039(03)01189-4



Scheme 2.

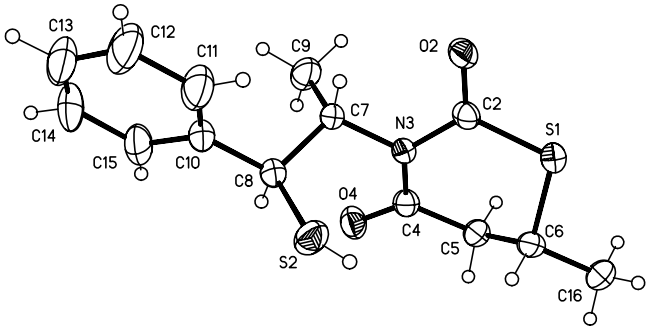
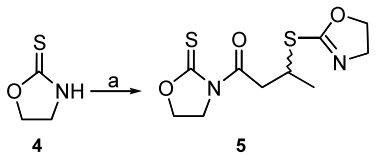


Figure 1. Molecular structure of heterocycle **2**.

tions for thiouracil containing molecules have been reported so far.[12,13]

The conformational analysis of heterocycle **2** shows that the *N*-methylene group has a preference to be in the plane and its bond angle is C2-N3-C7, 114.5°. The ^{1}H NMR spectrum of **2** at 323 K shows a doublet at δ 1.44 ppm for CH_3-16, which coalesces at 304 K ($\Delta G^{\neq} =$ 15.6 Kcal mol^{-1}), a dynamic behavior that may be attributed to C-6 interconversion.[14] In the solid state one conformation is stabilized corresponding to a screw-boat at C-6, as observed by X-ray diffraction.

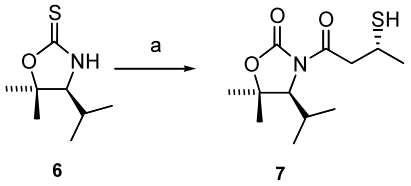
Our next task involved the preparation of the achiral oxazolidinethione **4** in quantitative yield.[15] This was deprotonated with NaH followed by acylation with 0.5 equiv. of *trans*-crotonyl chloride to afford **5** in 70% yield as a white solid which decomposes at 286°C (Scheme 3). The addition of a controlled quantity of



Scheme 3. *Reagents and conditions*: (a) NaH (1.1 equiv.), THF, 0°C, 45 min, *trans*-crotonyl chloride (0.5 equiv.), 0°C, 1 h.

trans-crotonyl chloride was realized so that the rest of the oxazolidinethione **4** should react in situ by a Michael addition at the beta position of the α,β-unsaturated system to give the sulfide **5**.

In order to establish if the new chiral auxiliary[9] **6** behaved like nucleophile (S$^-$) carrier molecule, the reaction was performed under the conditions described above (Scheme 4).



Scheme 4. *Reagents and conditions*: (a) NaH (1.1 equiv.), THF, 0°C, 45 min, *trans*-crotonyl chloride (0.5 equiv.), 0°C, 1 h, H_2O.

In this case the reaction afforded the β-mercapto adducts **7** in quantitative yield[16] as a (80:20) diastereomeric mixture (by ^{13}C NMR) and unreacted oxazolidinethione **6**. The obtention of the adduct **7** can be explained by in situ formation of the corresponding *N*-enoyl oxazolidinethione, followed by intramolecular sulfur atom transfer to the unsaturated system.[8,9] The Michael addition product was undetected due to the fact that the intramolecular attack is favored over the intermolecular one, probably because of steric hindrance.

In conclusion, we propose that the oxazolidinethione structure besides acting as a chiral auxiliary, can behave as a source of the nucleophile (S$^-$), although this ability can be affected by steric hindrance of its substituents in C4 and C5. This novel reaction has potential applications in heterocyclic synthesis.

Acknowledgements

The authors gratefully acknowledge financial support from CONACyT (Project J35098-E).

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10. Compound **2**: ^{1}H NMR (400 MHz, 323 K, CD_3OD): δ 7.45–7.32 (m, 5H, aromatic), 5.62 (d, 1H, $J=11.0$, H-8), 5.37 (m, 1H, H-6), 3.63 (m, 1H, H-7), 3.16 (dd, 1H, $J=15.7$, 3.3, H-5), 2.90 (dd, 1H, $J=16.1$, 9.2, H-5), 1.44 (d, 3H, $J=6.6$, CH_3-9), 1.13 (d, 3H, $J=7.0$, CH_3-16). Anal. calcd for $C_{14}H_7NO_2S_2$: C, 56.92; H, 5.80; N, 4.74. Found: C, 56.60; H, 5.40; N, 4.88.
11. *Crystal data for* **2**: $C_{14}H_{17}NO_2S_2$, $M=295.41$, colorless irregular, $0.70\times0.40\times0.14$ mm^3, space group $P2_12_12_1$, cell parameters $a=5.7711(9)$, $b=9.5575(12)$, $c=26.839(3)$ Å, $Z=4$, $D_{calcd}=1.325$ g cm^{-3}. 3234 reflections collected on a Bruker P4 diffractometer at room temp., with the Mo-$K\alpha$ radiation ($\lambda=0.71073$ Å) in the range $2\theta=4$–50°, of which 2599 are unique ($R_{int}=0.030$). 172 variables refined:[17] $R_1=0.0605$ [2189 data with $I>2\sigma(I)$] and $wR_2=0.1807$ [all data]. Absolute configuration based on the refinement of a Flack parameter:[18] $\chi=-0.05$ (17) for 1052 Friedel pairs measured. Complete data have been deposited with the CCDC, reference 206889. Structure factors and raw files are available on request to authors.
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