Tetrahedron Letters Vol.30,No.12,pp 1527-1528 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF ENANTIOMERICALLY PURE 2,3-DISUBSTITUTED ISOXAZOLIDIN-5-ONES

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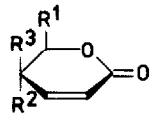
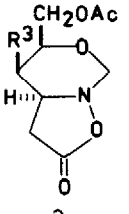
Abstract. Conjugate addition-rearrangement of *N*-substituted hydroxylamines to α,β-unsaturated sugar δ-lactones provides a short and effective route to title compounds.

Despite the interesting heterocyclic skeleton of isoxazolidin-5-ones, having a potential synthetic and pharmacological value, there are only a few reports on their synthesis.[1,2,3] In recent years conjugate addition of *N*-substituted hydroxylamines to α,β-unsaturated esters, followed by cyclization of the adduct to isoxazolidin-5-ones, has attracted attention of several laboratories.[2,3,4]

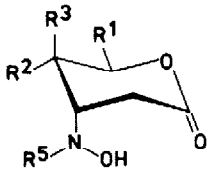
In the course of our studies leading to β-lactams from α,β-unsaturated sugar lactones, we have found that benzylhydroxylamine can be added to the double bond of the lactone with high stereoselectivity.[5] On the other hand, in the presence of formaldehyde, hydroxylamine has been shown to react with 1 to stereospecifically produce bicyclic compounds 2, most likely *via* the Michael adduct 3.[6] These results have prompted us to investigate the synthesis of 2,3-disubstituted isoxazolidin-5-ones 4, based on addition of hydroxylamines 5 to compounds 1.



1a : $R^1=R^2=R^3=H$
1b : $R^1=CH_2OAc, R^2=R^3=H$
1c : $R^1=CH_2OAc, R^2=OAc, R^3=H$
1d : $R^1=CH_2OAc, R^2=H, R^3=OAc$

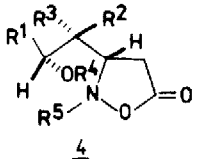


2 : $R^3=H, OAc$



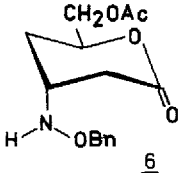
3

R^5NHOH
5 : $R^5=CH_3, C_6H_{11}, CH_2C_6H_4OCH_3$



4

$R^1=H, CH_2OAc$
$R^2, R^3=H, OAc$
$R^4=H, Sit\text{-}BuMe_2, Sit\text{-}BuPh_2, Ac$
$R^5=CH_3, C_6H_{11}, CH_2C_6H_4OCH_3$



6

The lactone 1 (0.5 mmol) prepared by the known method[7] was dissolved in abs. ethanol (5 ml) and was treated with 5 (0.5 mmol) at r.t. for 3 hrs. After evaporation of solvent, the adduct was isolated by chromatography or crystallization in a good or moderate yield; subsequently it was acetylated or silylated by a standard method and then identified spectrally and analytically.[8]

Addition of hydroxylamine 5 proceeds stereospecifically *anti* with respect to the terminal acetoxymethyl group (axial approach[9]), producing reactive adducts 3 which have a *N*-hydroxyl group suitably located for reacting with the lactone carbonyl group. The geometry of 3

plays a decisive role in easy formation of the isoxazolidin-5-one ring. Opening of the lactone ring produces compounds 4 with S-configuration at the C-3 isoxazolidine carbon atom when R^2 and R^3 are hydrogen atoms, whereas the R-configuration is obtained when R^2 or R^3 is OAc group. Determination of the configuration of 4 was based on our earlier assignments made for the *O*-benzylhydroxylamine adduct 6[5] and on X-ray crystal analysis of compound 2 (R^3=H)[6].

The procedure described herein presents a general route for the preparation of enantiomerically pure 2,3-disubstituted isoxazolidin-5-ones which can be utilized in the synthesis of selected structures, e.g. β-amino acids and β-lactams. It is also noteworthy, that this route does not require a strong base catalyzed rearrangement of the hydroxylamine Michael adduct.[2,3,4]

Acknowledgement. This work was supported by the Polish Academy of Sciences grant CPBP-01.13.

REFERENCES AND NOTES

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8. Selected analytical and spectral data for representative compounds 4:
4 (R^1=R^2=R^3=H, R^4=TBDPS, R^5=CH_3): 78%; m.p. 70-72°C; IR (film): 1795 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): 1.69, 1.89 (2m, 2H, $-CH_2-$), 2.57 (dd, 1H, J 10.6, 17.1 Hz, H-4), 2.78 (dd, 1H, J 6.9 Hz, H-4′), 2.85 (s, 3H, NCH_3), 3.31 (bs, 1H, H-3), 3.71, 3.78 (2m, 2H, $-CH_2O-$).
4 (R^1=CH_2OAc, R^2=R^3=H, R^4=TBDMS, R^5=C_6H_{11}): 73%; syrup; $[\alpha]_D$ -85.0° (*c* 1.5, CH_2Cl_2); IR (KBr): 1795 (C=O), 1735 cm^{-1}(Ac); ^{1}H-NMR ($CDCl_3$): 1.70, 1.88 (2ddd, 2H, $-CH_2-$), 2.07 (m, 1H, H-3), 3.94 (m, 1H, =CHO-), 3.97-4.05 (m, 2H, $-CH_2OAc$).
4 (R^1=CH_2OAc, R^2=H, R^3=OAc, R^4=TBDPS, R^5=$CH_2C_6H_4OCH_3$): 68%; syrup; $[\alpha]_D$ -51.2° (*c* 1, CH_2Cl_2); IR (film): 1790 (C=O), 1750 cm^{-1} (Ac); ^{1}H-NMR ($CDCl_3$): 2.19 (dd, 1H, J 3.4, 18.0 Hz, H-4), 2.38 (dd, 1H, J 9.1 Hz, H-4′), 3.77 (m, 1H, H-3), 3.78 (s, 3H, OCH_3), 3.81 (dd, 1H, J 6.3, 11.9 Hz, CH_AH_BOAc), 3.88 (dd, 1H, J 3.9 Hz, CH_AH_BOAc), 4.03, 4.08 (2d, 2H, $-NCH_2-$), 4.06 (m, 1H, =CHOTBDPS), 4.97 (dd, 1H, J 4.8, 5.9 Hz, $=CH_AH_BCHOAc$).
4 (R^1=CH_2OAc, R^2=OAc, R^3=H, R^4=Ac, R^5=$CH_2C_6H_4OCH_3$): 80%; syrup; $[\alpha]_D$ -42.0° (*c* 0.6, CH_2Cl_2); IR ($CHCl_3$): 1790 (C=O), 1750 cm^{-1} (Ac); ^{1}H-NMR ($CDCl_3$): 2.71 (dd, 1H, J 8.5, 17.5 Hz, H-4), 2.82 (dd, 1H, J 7.2 Hz, H-4′), 3.62 (ddd, 1H, J 3.1 Hz, H-3), 4.08, 4.19 (2d, 2H, $-CH_2N$), 4.13-4.21 (m, 2H, CH_2OAc), 5.18 (ddd, 1H, J 3.4, 5.0, 7.0 Hz, H-β), 5.24 (dd, 1H, H-α).
4 (R^1=CH_2OAc, R^2=R^4=H, R^3=OAc, R^5=$CH_2C_6H_4OCH_3$): 90%; m.p. 127-130°C; $[\alpha]_D$ -76.4° (c 1, CH_2Cl_2); IR (nujol): 3380 (OH), 1800 (C=O), 1750, 1745 cm^{-1}(Ac); ^{1}H-NMR ($CDCl_3$): 2.53 (dd, 1H, J 2.7, 17.9 Hz, H-2), 2.69 (dd, 1H, J 9.3 Hz, H-2′), 3.88 (dd, 1H, J 6.4, 11.6 Hz, CH_AH_BOAc), 3.89 (m, 1H, H-3), 3.96 (dd, 1H, J 4.8 Hz, CH_AH_BOAc), 4.04 (m, 1H, =CHOH), 4.10, 4.21 (2d, 2H, $=NCH_2-$), 4.95 (dd, 1H, J 3.0, 4.5 Hz, $=CHOAc$).
9. P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Oxford, 1983, pp. 221-241.

(Received in UK 6 February 1989)