Tetrahedron Letters, Vol. 33, No. 48, pp. 7413-7416, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

The Uncatalyzed Ring Opening of Hetaryloxides with Nitrogen Nucleophiles. A Dichotomy of Regioselectivity.

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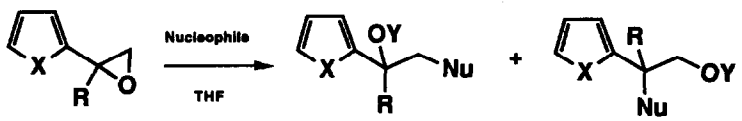
Key Words: Hetaryloxides, ring opening, aminoalcohols, nitrogen nucleophiles.

Abstract: *The uncatalyzed ring opening of the hetaryloxides 1, 2 and 3 with benzylamine and trimethylsilylazide has been studied being the observed regioselectivity different depending on the nucleophile used.*

The ring opening of oxiranes with nitrogen nuclophiles constitutes the most widely used method for the preparation of useful 1,2-aminoalcohols.[1] In the case of aryl oxides, the ring opening both with amines and azides needs catalysis[2] or severe reaction conditions.[3] In this paper we wish to account for our studies on the regioselective ring opening of furyl- and thienyl oxides with benzylamine and trimethylsilylazide in absence of catalysis. The ring opening of the three hetaryloxides **1**, **2** and **3**[4] with benzylamine gave, with total regioselectivity, the aminoalcohol arising from the nucleophilic attack on the less substituted carbon atom (Table, entries 1, 2 and 3).[5] On the other hand, reaction with trimethylsilylazide yields the opposite regioisomer as unique product (Table, entries 4, 5 and 6).



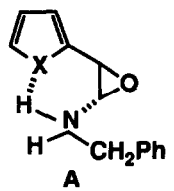
1-3 **4-9** **10-15**

1: X=O, R=H; **2**: X=S, R=H; **3**: X=O, R=Me

Table. Regioselectivity of the Ring Opening of Hetaryloxides with Nitrogen Nucleophiles.

Entry	Oxirane	Nucleophile	Y	Regiosel.[a]	Yield[b]	React.Time	Temperature
1	**1**	$PhCH_2NH_2$	H	**4/10**=100/0	25[c]	3 days	reflux THF
2	**2**	$PhCH_2NH_2$	H	**5/11**=100/0	70[c]	3 days	rt
3	**3**	$PhCH_2NH_2$	H	**6/12**=100/0	70[c]	12 days	rt
4	**1**	Me_3SiN_3	$OSiMe_3$	**7/13**=0/100	87[c]	4 days	rt
5	**2**	Me_3SiN_3	$OSiMe_3$	**8/14**=0/100	100[d]	4 days	rt
6	**3**	Me_3SiN_3	$OSiMe_3$	**9/15**=0/100	100[d]	5 days	0°C

a) Determined by ^{1}H-nmr. b) Isolated yield. c) Only the indicated regioisomer was obtained. The remaining material was a mixture of starting oxirane and unidentified products without observation of the other regioisomeric alcohol. For oxirane **1** see reference 5. In all cases purification was achieved by column chromatography on silica gel using as eluent mixtures of diferents proportions of n-hexane-AcOEt. Full details will be published elsewhere. d) Pure products were obtained directly as reaction crude. Manipulation of them (see text) did not need further purification.

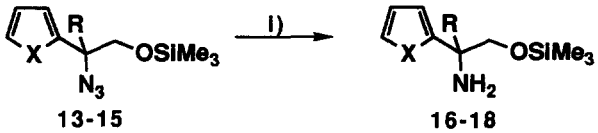


A

The regioselectivity of the reactions was determined as follows: compound **5** shows in ^{1}H-nmr spectra (300 MHz, DMSO-d_6) the hydroxylic proton as doublet (δ = 5.2 ppm) by coupling with the vicinal methyne proton. Regarding the aliphatic moiety, compounds **4-6** show related chemical shifts and splitting patterns, both in ^{1}H and ^{13}C-nmr. For compounds **13-15**,[6] desilylation[7] yields the related azidoalcohols which show in ^{1}H-nmr (DMSO-d_6) the hydroxylic proton as a triplet by coupling with the vicinal methylene protons.

The difference in behaviour between both nucleophiles could be tentatively ascribed to an "electrophilic anchimeric assistance" by the amine hydrogen giving a transition state like A.[8]

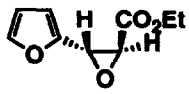
The compounds **13-15** were transformed in the related trimethylsilyloxyaminoderivatives, precursors of the corresponding aminoalcohols, by reduction of the azido group.[9]



13-15 **16-18**

13,16: X=O, R=H; **14,17:** X=S, R=H; **15,18:** X=O, R=Me
i) H_2/Pd-C 10%, 45 psi, AcOEt, rt

Adaptation of the method to the synthesis of ethyl α-hydroxy-β-amino-β-hetarylpropionate[10, 11] was performed starting from compound **19** as model.[12] Reaction of **19** with Me_3SiN_3 (THF, rt, 48 h) gave the R*S* compound **20**[13] as unique product. Subsequent hydrogenation of **20** (H_2/ Pd-C 10%, 45 psi, AcOEt, 5h) affords **21**[14] which was transformed in **22** (SiO_2/MeOH, rt).[15] The relative stereochemistry of compounds **20-22** was established by transformation of **21** into the β-lactam **23** by reaction with Me_3SiCl/ Et_3N followed by treatment with Bu^tMgCl/ Et_2O.[16] The stereochemistry of the β-lactam as cis was deduced from the value of $J_{3,4}$ = 4.5 Hz,[17] and from the multiplicity of H4 (dd, δ = 5.07 ppm, J_1 = 4.5 Hz, J_2 = 2.1 Hz) by coupling with the amide proton.



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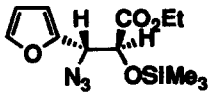

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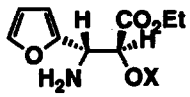
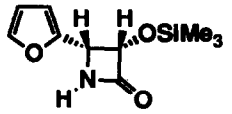


21 X=SiMe3, 22 X=H



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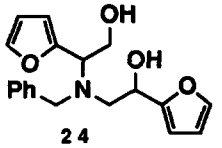
In summary, the addition of nitrogenated nucleophiles to hetaryl oxides occurs without catalysis and under mild conditions with opposite regioselectivity according to the nature of the nucleophilic agent (amine or azide). Standard manipulation of the trimethylsilylazide derivatives affords the hetarylaminoethanols in good yield. Adaptation of the method to carboethoxyhetaryloxides opens the way for the preparation of potentially useful α-hydroxy-β-amino-β-hetarylesters and the related β-lactams.

Acknowledgement: This work was supported by the C.I.C.Y.T. (Ministerio de Educación y Ciencia, Spain). Grant. nº PB87-0064 and for PharmaMar S.A.. We thank Prof. A. Gaset (E.N.S.C.T.) for valuable discussions.

REFERENCES AND NOTES

1. There is an enormous literature on the chemical and pharmacological properties of this class of compound. For a selected compilation, see D. J. Triggle in "Adrenergics: Catecholamines and Related Agents". Burger's Medicinal Chemistry. 4th Edition. M. E. Wolff. Ed. J. Wiley. 1981. Part III. Ch. 41. In addition, the β-aminoalcohol moiety is present in numerous natural products. See, for instance: a) D. Horton, J. D. Wander in "The Carbohydrates". W. Pigman and D. Horton Eds. Academic Press, N.Y. 1980. Vol. 1B. pp 643; b) J. Schubert, R. Schwesinger, H. Prinzbach *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 167.
2. For some selected, recent references, see: Aminolysis, M. Chini, P. Crotti, F. Macchia *J. Org. Chem.* **1991**, *56*, 5939 and references therein. Azidolysis, a) K. I. Sutowardoyo, M. Emziane, P. Lhoste, D. Sinou *Tetrahedron* **1991**, *47*, 1435 and references therein; b) A. Guy, J. Doussot, R. Garreau, A. Godefroy-Falguieres *Tetrahedron Asymmetry* **1992**, *3*, 247 and references therein.
3. Classical aminolysis procedure involving the direct heating of oxiranes with amines has some significant limitations in reactions with poorly nucleophilic amines. For a comprehensive study with special regard to the side reactions see N. S. Enikolopian *Pure Appl. Chem.* **1976**, *48*, 317. Azidolysis is carried out under alkaline conditions and usually requires high temperatures and long reaction times. Side reactions induced by the alkaline conditions gave unsatisfactory results with respect both to regioselectivity and chemoselectivity. For selected references, see: a) M. Neitzberg, Z. Aizenshat, P. Jershelmy, J. Blum *J. Org. Chem.* **1980**, *45*, 4252; b) R. Schwesinger, M. Breuninger, B. Gallenkamp, K. H. Müller, D. Hunkler, H. Prinzbach *Chem. Ber.* **1980**, *113*, 3127; c) E. P. Müller *Helv. Chim. Acta* **1982**, *65*, 1617.
4. M. E. Borredon, M. Delmas, A. Gaset *Bull. Soc. Chim. France* **1987**, 1033.
5. In the reaction of **1** with benzylamine, a by-product was isolated (25% yield) whose spectroscopic data are consistent with a compound of double addition of **1** to benzylamine. The structure of this compound is probably **24**.



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6. Reaction of **1** with trimethylsilylazide in the presence of aluminium isopropoxide and titanium isopropoxide has been described giving ratio **7**/**13** = 1/99 (overall yield 74%). See reference 2a.
7. Desilylation was performed by reaction with HCl (traces)/MeOH for compounds **13** and **15**. See reference 2a. Compound **14** was desilylated by treatment with SiO_2/MeOH, rt. In all cases yields were quantitative.
8. For related phenomena, see: a) H. Sulzer, J. Widmer *Helv. Chim. Acta* **1977**, *60*, 1676; b) D. R. Burfiel, S. Gau, R. H. Smithers *J. Chem. Soc. Perkin 1* **1977**, 666.

9. See, J. N. Denis, A. Correa, A. E. Greene *J. Org. Chem.* **1990**, *55*, 1957. Selected spectroscopic data and isolated yields: Compound **16**: Yield 90%. ^{1}H-nmr ($CDCl_3$, 300 MHz): 7.28 (dd, 1H, J_1 = 0.9 Hz, J_2 = 2.1 Hz), 6.25 (dd, 1H, J_1 = 2.1 Hz, J_2 = 3.0 Hz), 6.16 (d, 1H, J = 3.0 Hz,), 3.99-3.94 (m, 1H), 3.78 (dd, 1H, J_1 = 3.9 Hz, J_2 = 9.9 Hz), 3.57 (dd, 1H, J_1 = 7.5 Hz, J_2 = 9.9 Hz), 2.59 (broad, 2H), -0.07 (s, 9H). ^{13}C-nmr ($CDCl_3$, 80 MHz): 155.43, 141.38, 110.01, 105.52, 66.00, 51.44, 0.73. Compound **17**: Yield 90%. ^{1}H-nmr ($CDCl_3$, 300 MHz): 7.18 (t, 1H, J = 2.9 Hz), 6.94 (d, 1H, J = 3.7 Hz), 4.31 (dd, 1H, J_1 = 3.9 Hz, J_2 = 8.3 Hz), 3.74 (dd, 1H, J_1 = 3.9 Hz, J_2 = 9.8 Hz), 3.52 (dd, 1H, J_1 = 8.3 Hz, J_2 = 9.8 Hz), 1.89 (s, 2H), 0.10 (s, 9H). ^{13}C-nmr ($CDCl_3$, 80 MHz): 146.81, 126.43, 123.86, 123.33, 68.92, 53.40, -0.65. Compound **18**: Yield 75%. ^{1}H-nmr ($CDCl_3$, 300 MHz): 7.28 (d, 1H, J = 0.9 Hz), 6.25 (t, 1H, J = 3.0 Hz), 6.13 (d, 1H, J = 3.0 Hz), 3.83 (d, 1H, J = 9.6 Hz), 3.51 (d, 1H, J = 9.6 Hz), 1.82 (s, 2H), 1.33 (s, 3H), 0.01 (s, 9H). ^{13}C-nmr ($CDCl_3$, 80 MHz): 159.70, 140.94, 109.87, 104.49, 70.06, 53.78, 24.26, -0.75.
10. For the synthesis and biological importance of α-hydroxy-β-aminoacids, see ref. 9 and also: a) J . M. Chong, K. B. Sharpless *J. Org. Chem.* **1985**, *50*, 1560; b) J. -N. Denis, A. E. Greene, A. A. Serra, M. -J. Luche *J. Org. Chem.* **1986**, *51*, 46; c) T. Ohta, S. Shiokawa, R. Sakamoto S. Nozoe *Tetrahedron Letters* **1990**, *31*, 7329; d) Y. Takemoto, T. Matsumoto, Y. Ito, S. Terashima *Tetrahedron Letters* **1990**, *31*, 217; e) C. Palomo, A. Arrieta, F. P. Cossio, J. M. Aizpurua, A. Mielgo, N. Aurrekoetxea *Tetrahedron Letters* **1990**, *31*, 6429; f) I. Ojima, I. Habus, M. Zhao, G. -I. Georg, L. R. Jayashinge *J. Org. Chem.* **1991**, *56*, 1681; g) E. J. Corey, S. Choi *Tetrahedron Letters* **1991**, *32*, 2857; h) Y. Kobayashi, Y. Takemoto, T. Kamijo, H. Harada, Y. Ito, S. Terashima *Tetrahedron* **1992**, *48*, 1853.
11. For recent references on reaction of azides with epoxyesters, see: a) J. Legters, L. Thijs, B. Zwanenburg *Tetrahedron* **1991**, *47*, 5287; b) S. Saito, H. Takahasi, T. Ishikawa, T. Morikawe *Tetrahedron Letters* **1991**, *32*, 667; c) J. Legters, L. Thijs, B. Zwanenburg *Rec. Trav. Chim. Pays Bas* **1992**, *111*, 1; d) J. Legters, E. Vandienst, L. Thijs, B. Zwanenburg *Rec. Trav. Chim. Pays Bas* **1992**, *111*, 69.
12. K. O. Koua, M. E. Borredon, M. Delmas, A. Gaset *Synth. Comm.* **1987**, *1*, 1593.
13. Yield 50%. ^{1}H-nmr ($CDCl_3$, 300 MHz): 7.42-7.41 (m, 1H), 6.40-6.37 (m, 2H), 4.77 (d, 1H, J = 4.8 Hz), 4.55 (d, 1H, J = 4.8 Hz), 4.18 (dq, 2H, J_1 = 0.9 Hz, J_2 = 7.2 Hz), 1.23 (t, 3H, J = 7.2 Hz), 0.12 (s, 9H). ^{13}C-nmr ($CDCl_3$, 80 MHz): 170.18, 148.91, 142.65, 110.39, 108.77, 74.39, 61.30, 60.88, 13.89, -0.44.
14. Yield 90%. ^{1}H-nmr ($CDCl_3$, 300 MHz): 7.31 (dd, 1H, J_1 = 0.9 Hz, J_2 = 1.8 Hz), 6.28 (dd, 1H, J_1 = 1.8 Hz, J_2 = 3.3 Hz), 6.20 (dt, 1H, J_1 = 0.9 Hz, J_2 = 3.3 Hz), 4.43 (d, 1H, J = 3.6 Hz), 4.32 (dd, 1H, J_1 = 0.9 Hz, J_2 = 3.6 Hz), 4.17 (dq, 2H, J_1 = 3.0 Hz, J_2 = 6.9 Hz), 1.24 (t, 3H, J = 6.9 Hz), -0.03 (s, 9H). ^{13}C-nmr ($CDCl_3$, 80 MHz): 171.72, 155.43, 141.33, 110.19, 106.27, 74.47, 61.00, 53.35, 13.06, -0.59.
15. Yield 99%. ^{1}H-nmr ($CDCl_3$, 300 MHz): 7.36-7.35 (m, 1H), 6.32 (dd, 1H, J_1 = 2.8 Hz, J_2 = 3.3 Hz), 6.26 (d, 1H, J = 3.3 Hz), 4.46 (d, 1H, J = 3.3 Hz), 4.29 (d, 1H, J = 3.3 Hz), 4.25 (q, 2H, J = 7.2 Hz), 2.65 (broad, 3H), 1.27 (t, 3H, J = 7.2 Hz). ^{13}C-nmr ($CDCl_3$, 80 MHz): 172.92, 155.15, 141.71, 110.22, 106.11, 72.89, 61.88, 52.36, 14.03.
16. A. V. Rama Rao, M. K. Gurjar, B. Ashok *Tetrahedron Asymmetry* **1991**, *2*, 255. Compound **23**: Yield 90%. ^{1}H-nmr ($CDCl_3$, 300 MHz): 7.42 (t, 1H, J = 1.5 Hz), 6.67 (broad, 1H), 6.39 (d, 2H, J = 1.5 Hz), 5.07 (dd, 1H, J_1 = 2.1 Hz, J_2 = 4.5 Hz), 4.81 (d, 1H, J = 4.5 Hz), -0.01 (s, 9H). ^{13}C-nmr ($CDCl_3$, 80 MHz): 169.52, 150.24, 142.59, 110.56, 109.18, 79.24, 53.08, -0.49.
17. See ref. 10e and also T. Kawabata, A. Itoh, A. Hiyama *Tetrahedron Letters* **1989**, *30* , 4837.

(Received in UK 7 September 1992)