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Transformations Starting from Biotechnologically Available Materials, Part 2 [1]: First Example of a Direct Conversion of Spirooxiranes into Enamines

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Summary. An unpredecent formation of enamines in the reaction of 5-aryl-1-oxa-5-azaspiro[2.4]heptane-4,6-diones with morpholine and piperidine is reported. The transformations proceed via corresponding β-aminoalcohols which were detected by ^{13}C-NMR.

Keywords. Enamines; Nucleophilic ring opening; Spirooxiranes.

Transformationen von biotechnisch verfügbarem Material, 2. Mitt.: Erstes Beispiel für die direkte Konversion von Spirooxiranen in Enamine

Zusammenfassung. Es wird über die Bildung von Enaminen aus der Reaktion von 5-Aryl-1-oxa-5-azaspiro[2.4]heptan-4,6-dionen mit Morpholin oder Piperidin berichtet. Die Transformation verläuft über die entsprechenden β-Aminoalkohole, die mittels ^{13}C-NMR nachgewiesen werden können.

Introduction

5-Aryl-1-oxa-5-azaspiro[2.4]heptane-4,6-diones (**1**) represent a class of novel spirooxiranes prepared from corresponding N-aryl-itaconimides **2** by treatment with peroxytrifluoroacetic acid [1]. The introduction of a new reactive centre into the molecule of the parent compound **2** offers an opportunity for further synthetic manipulations. Undoubtedly, nucleophilic attack on ring carbon atoms is the most important reaction of oxirane derivatives. The stereochemistry and mechanistic aspects of such cleavages have been reviewed [2] and have been studied in particular with oxygen and nitrogen nucleophiles [3], [4].

Here we report an unusual ring opening of spirooxiranes **1** with secondary amine nucleophiles.

Results and Discussion

Upon treatment with morpholine in refluxing ethanol the 5-phenyl derivative **1a** gave a compound **3a** whose elemental composition ($C_{15}H_{16}N_2O_3$) indicated a loss

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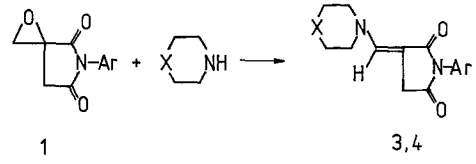
of H_2O from the expected β-aminoalcohol. In addition, no hydroxyl band was detected in the IR spectrum. Also the absence of an AB quartet for a methylene group arising from the original three-membered oxygen ring [1] in the ^{1}H-NMR spectrum excluded the aminoalcohol. On the other hand, a one proton signal at δ_H 7.27 along with the corresponding low-field carbon resonance (δ_C 143.4) in the NMR spectra can be attributed to the acylic enamine moiety [5]. The value of one-bond ^{13}C-^{1}H coupling constant (^1J = 166 Hz) is typical of morpholino ethylenes [6], too. Hence the spectral data are compatible with the structure of 2-(4-morpholinomethylidene)-N-phenyl-succinimide (**3a**). Analogous reactions were observed for a number of aryl substituted spirooxiranes **1** (Scheme 1). Piperidine reacted with spirooxiranes **1** in a similar manner to afford enamino derivatives **4**. With piperazine only a small amount of the 1 : 1 product was obtained.

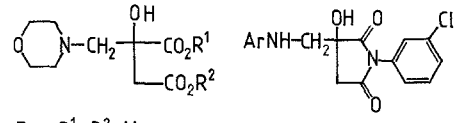


1 3,4

1,3	Ar	X
a	C_6H_5	O
b	4-ClC_6H_4	O
c	3-ClC_6H_4	O
d	3-$NO_2C_6H_4$	O

4	Ar	X
a	3-ClC_6H_4	CH_2
b	3-$NO_2C_6H_4$	CH_2

Scheme 1



5a $R^1 = R^2 = Me$
5b $R^1 = Me$, $R^2 = H$ or $R^1 = H$, $R^2 = Me$

6a Ar = 4-ClC_6H_4
6b Ar = 3-ClC_6H_4

Scheme 2

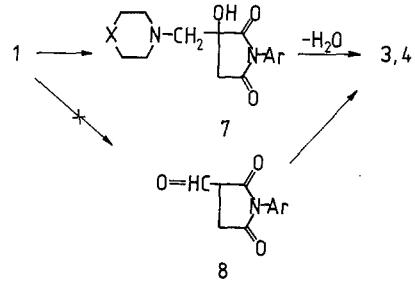
The configuration at the enamine double bond was examined for the derivative **3b** only because the ^{13}C chemical shifts (being extremely sensitive to spatial changes [7]) were identical for both olefinic carbons and adjacent methylene group in all synthesized compounds. Thus, the (*Z*)-geometry of the product **3b** was determined on the basis of NOE enhancement between the NCH and CH_2 protons.

The reaction of dimethyl epoxy itaconate with morpholine furnished under analogous conditions β-aminoalcohols **5a** and **5b** in approximately a 3 : 1 ratio, as estimated by GC/MS [8] (Scheme 2).

An attempted conversion of oxirane **1c** with *tert.*-butylamine, as a representative of primary alkylamines, led only to decomposition products. By contrast, when 4-chloroaniline was employed only ring opening reaction occurred to give 2-hydroxy substituted succinimide **6a**. An analogous derivative **6b** was obtained from 3-chloro-aniline (Scheme 2).

The direct conversion of oxiranes **1** into enamines **3** and **4** is unusual and without literature precedence. In all known cases only formation of the corre-

sponding β-aminoalcohols has been described [3, 4, 9] and often even more vigorous conditions were necessary [10]. The enamine formation can proceed by cleavage of spirooxiranes **1** at the CH_2 terminus followed by dehydration of the intermediate **7**. Presumably the initial elimination product from the aminoalcohol **7** is a kinetically favoured maleimide, which can then undergo isomerization to the observed enamines **3** or **4**. This strongly suggests that the reason for the formation of the enamines in the reaction reported here is the presence of the carbonyl group β to the tertiary hydroxyl. Nevertheless, an alternative route through an oxirane rearrangement [11] to an aldehyde **8** cannot be excluded (Scheme 3).



Scheme 3

In order to provide better insight into the mechanistic pathway an attempt was made to determine an intermediate. However, besides the enamines only traces of anilines arising from the imide ring scission along with considerable amounts of tars were isolated by column chromatography.

Therefore, the reaction course of **1 c** with morpholine was monitored by ^{13}C-NMR spectroscopy at room temperature in deutero acetone. Thereby at δ_C 56.6 a signal was observed for a fast formed intermediate which disappeared slowly during 1 h. The latter can be assigned to the methylene group bearing the morpholine residue in the transient β-aminoalcohol **7**, because the chemical shifts for the $NHCH_2$ moiety in similar derivatives **6 a** and **6 b** were found near δ_C 50. Although the rate determining step is the elimination of water, the presence of the signal belonging to the enamine carbon (δ_C 145.7) for **3 c** was observed in a relatively short time interval (ca. 20 min). On the other hand, no evidence for the alternative aldehydic species **8** was found.

Experimental Part

Melting points were determined on a Boetius micro hot-stage apparatus. IR spectra were measured with a M-80 (Zeiss, Jena) spectrophotometer. ^1H- and ^{13}C-NMR spectra were run with a Varian VXR-300 instrument. Mass spectra were recorded with a Jeol D-100 double focussing spectrometer (75 eV) using a direct-probe inlet.

General Procedure for the Preparation of Enamines **3 a–d, 4 a, b** *and Aminoalcohols* **6 a, b**

A suspension of the corresponding spiro-oxirane **1 a–d** (0.005 mol) and a secondary amine (0.02 mol) or aniline (0.01 mol) in ethanol (50 ml) was refluxed overnight. The dark solution was reduced to a smaller volume in vacuo and allowed to crystallize. The oily residue obtained after evaporation of the solvent (**6 a, b**) was triturated with toluene. The separated material was recrystallized from ethanol (enamines) or toluene (aminoalcohols).

2-(4-Morpholinomethylidene)-N-phenylsuccinimide (**3 a**)

Yield 0.48 g (35%), m.p. 189–191°C. IR ($CHCl_3$): ν = 1 694 (C=O), 1 623 cm^{-1} (C=C). ^{1}H-NMR (acetone-d_6): δ = 3.56 (t, 4 H, 2 CH_2N), 3.59 (d, ^4J = 1.5 Hz, 2 H, imide CH_2), 3.73 (t, 4 H, 2 CH_2O), 7.27 (d, ^4J = 1.2 Hz, 1 H, NCH=), 7.36 (m, 3 H, H_{Ar}), 7.45 (m, 2 H, H_{Ar}). ^{13}C-NMR (acetone-d_6): δ = 33.6 (t, CH_2), 50.4 (t, CH_2N), 66.9 (t, CH_2O), 89.9 (s, olefine C), 127.4, 128.9 (d, C_{ortho} and C_{meta}), 127.7 (d, C_{para}), 134.5 (s, C_{ipso}), 143.4 (d, NCH=), 171.8 (s, C=O), 173.8 (s, C=O). MS (75 eV): *m/z* = 272 (M^+). $C_{15}H_{16}N_2O_3$ (272.3). Calcd. C 66.16, H 5.92, N 10.29; found C 66.31, H 5.79, N 10.42.

2-(4-Morpholinomethylidene)-N-4-chlorophenylsuccinimide (**3 b**)

Yield: 0.52 g (34%), m.p. 173–176°C. IR ($CHCl_3$): ν = 1 694 (C=O), 1 623 cm^{-1} (C=C). ^{1}H-NMR ($CDCl_3$): δ = 3.47 (t, 4 H, 2 CH_2N), 3.52 (d, ^4J = 0.6 Hz, 2 H, imide CH_2), 3.75 (t, 4 H, 2 CH_2O), 7.27 (d, ^4J = 0.6 Hz, 1 H, NCH=), 7.31 (d, 2 H, H_{Ar}), 7.43 (d, 2 H, H_{Ar}). ^{13}C-NMR ($CDCl_3$): δ = 33.36 (t, CH_2), 49.85 (t, CH_2N), 66.29 (t, CH_2O), 88.64 (s, olefine C), 127.61, 128.78 (d, C_{Ar}), 131.12, 133.16 (s, C_{Ar}), 143.34 (d, NCH=), 171.19 (s, C=O, 173.06 (s, C=O). $C_{15}H_{15}N_2O_3Cl$ (306.7). Calcd. C 58.73, H 4.93, N 9.13; found C 58.54, H 5.09, N 9.01.

2-(4-Morpholinomethylidene)-N-3-chlorophenylsuccinimide (**3 c**)

Yield: 0.58 g (38%), m.p. 197–199°C. IR ($CHCl_3$): ν = 1 700 (C=O), 1 625 cm^{-1} (C=C). ^{1}H-NMR ($CDCl_3$): δ = 3.45 (t, 4 H, 2 CH_2N), 3.52 (d, ^4J = 1.5 Hz, 2 H, imide CH_2), 3.74 (t, 4 H, 2 CH_2O), 7.25–7.41 (m, 5 H, 4 H_{Ar} + NCH=). ^{13}C-NMR ($CDCl_3$): δ = 33.53 (t, CH_2), 50.08 (t, CH_2N), 66.46 (t, CH_2O), 88.81 (s, olefine C), 124.73, 126.78, 127.89, 129.70 (d, C_{Ar}), 133.91, 134.21 (s, C_{Ar}), 143.57 (d, NCH=), 171.24 (s, C=O), 173.11 (s, C=O). $C_{15}H_{15}N_2O_3Cl$ (306.7). Calcd. C 58.73, H 4.93, N 9.13; found C 58.67, H 4.79, N 9.08.

2-(4-Morpholinomethylidene)-N-3-nitrophenylsuccinimide (**3 d**)

Yield: 0.65 g (41%), m.p. 185–186°C. IR (KBr): ν = 1 695(C=O), 1 645 (C=C), 1 535 (NO_2), 1 350 cm^{-1} (NO_2). ^{1}H-NMR (*DMSO-d*$_6$): δ = 3.51 (br s, 4 H, 2 CH_2N), 3.64 (br s, 6 H, 2 CH_2O + imide CH_2), 7.34 (s, 1 H, NCH=), 7.77 (t, 1 H_{Ar}), 7.83 (d, 1 H, H_{Ar}), 8.21 (d, 1 H, H_{Ar}), 8.30 (s, 1 H, H_{Ar}). ^{13}C-NMR (*DMSO-d*$_6$): δ = 33.20 (t, CH_2), 49.80 (t, CH_2N), 66.15 (t, CH_2O), 88.28 (s, olefine C), 121.45, 122.06, 129.97, 133.28 (d, C_{Ar}), 134.22 (s, C_{Ar}), 143.53 (d, NCH=), 147.63 (s, C_{Ar}), 170.46 (s, C=O), 173.34 (s, C=O). $C_{15}H_{15}N_3O_5$ (317.30). Calcd. C 56.78, H 4.76, N 13.24; found C 56.99, H 4.87, N 13.02.

2-(1-Piperidinomethylidene)-N-3-chlorophenylsuccinimide (**4 a**)

Yield: 0.43 g (28%), m.p. 151–152°C. IR (KBr): ν = 1 690 (C=O), 1 615 cm^{-1} (C=C). ^{1}H-NMR ($CDCl_3$): δ = 1.63 (br s, 6 H, 3 CH_2), 3.38 (br s, 4 H, 2 CH_2N), 3.52 (s, 2 H, imide CH_2), 7.26–7.42 (m, 5 H, 4 H_{Ar} + NCH=). ^{13}C-NMR ($CDCl_3$): δ = 23.63 (t, CH_2), 25.98 (t, CH_2), 33.55 (t, CH_2), 51.40 (t, CH_2N), 86.51 (s, olefine C), 124.62, 126.61, 127.46, 129.48 (d, C_{Ar}), 133.91, 133.95 (s, C_{Ar}), 143.79 (d, NCH=), 171.25 (s, C=O), 173.37 (s, C=O). $C_{16}H_{17}N_2O_2Cl$ (304.8). Calcd. C 63.05, H 5.62, N 9.19; found C 62.89, H 5.48, N 9.33.

2-(1-Piperidinomethylidene)-N-3-nitrophenylsuccinimide (**4 b**)

Yield: 0.32 g (20%), m.p. 174–177°C. IR (KBr): ν = 1 690 (C=O), 1 530 (NO_2), 1 349 cm^{-1} (NO_2). ^{1}H-NMR (*DMSO-d*$_6$): δ = 1.59 (br s, 6 H, 3 CH_2), 3.44 (br s, 4 H, 2 CH_2N), 3.62 (s, 2 H, imide CH_2), 7.32 (s, 1 H, NCH=), 7.78 (t, 1 H, H_{Ar}), 7.82 (d, 1 H, H_{Ar}), 8.21 (d, 1 H, H_{Ar}), 8.23 (s, 1 H, H_{Ar}).^{13}C-NMR (*DMSO-d*$_6$): δ = 23.44 (t, CH_2), 26.03 (t, CH_2), 33.29 (t, CH_2), 50.50 (t, CH_2N), 86.77 (s, olefine

C), 121.36, 121.92, 129.91, 133.20 (d, C_{Ar}), 134.34 (s, C_{Ar}), 143.68 (d, NCH=), 147.50 (s, C_{Ar}), 170.31 (s, C=O), 173.35 (s, C=O). MS (75 eV): m/z=315 (M^+). $C_{16}H_{17}N_3O_4$ (315.3). Calcd. C 60.94, H 5.43, N 13.33; found C 61.13, H 5.37, N 13.21.

2-Hydroxy-2-(4-chloroanilinomethyl)-N-3-chlorophenylsuccinimide (**6 a**)

Yield: 0.95 g (52%), m.p. 109–112°C. IR (KBr): ν=3 465 (OH), 3 380 (NH), 1 696 cm^{-1} (CO). ^{1}H-NMR (acetone-d_6):δ=2.96 and 3.50 (AB q, ^2J=18.0 Hz, 2 H, imide CH_2), 3.58 (dd, ^2J=13.8 Hz, ^3J=5.4 Hz, 1 H, CH_2), 3.85 (dd, ^2J=13.8 Hz, ^3J=7.5 Hz, 1 H, CH_2), 5.50 (s, 2 H, OH+NH), 6.76 (d, 2 H, H_{Ar}), 7.12 (d, 2 H, H_{Ar}), 7.18 (m, 2 H, H_{Ar}), 7.45 (m, 2 H, H_{Ar}). ^{13}C-NMR (acetone-d_6): δ=41.56 (t, CH_2), 50.37 (t, CH_2N), 76.13 (s, C−OH), 114.90 (d, C_{Ar}), 122.06 (s, C_{Ar}), 126.10, 127.55, 129.05, 129.61, 130.93 (d, C_{Ar}), 134.38, 134.49, 147.97 (s, C_{Ar}), 173.41 (s, C=O), 178.56 (s, C=O). $C_{17}H_{14}N_2O_3Cl$ (365.2). Calcd. C 55.90, H 3.86, N 7.67; found C 56.11, H 4.02, N 7.58.

2-Hydroxy-2-(3-chloroanilinomethyl)-N-3-chlorophenylsuccinimide (**6 b**)

Yield: 1.19 g (65%), m.p. 125–128°C. IR (KBr): ν=3 429 (OH), 3 378 (NH), 1 698 cm^{-1} (C=O). ^{1}H-NMR (acetone-d_6): δ=2.98 and 3.26 (AB q, ^2J=18.0 Hz, 2 H, imide CH_2), 3.62 and 3.87 (AB q, ^2J=13.0 Hz, 2 H, CH_2), 5.54 (br s, 1 H, OH or NH), 5.63 (br s, 1 H, NH or OH), 6.68 (m, 2 H, H_{Ar}), 6.81 (m, 1 H, H_{Ar}), 7.11 (m, 1 H, H_{Ar}), 7.22 (m, 2 H, H_{Ar}), 7.46 (m, 2 H, H_{Ar}). ^{13}C-NMR (acetone-d_6): δ=41.08 (t, CH_2), 49.62 (t, CH_2N), 75.60 (s, C−OH), 111.69, 112.69, 117.25, 125.56, 127.02, 128.60, 130.42, 130.71 (d, C_{Ar}), 133.98, 134.86, 150.07 (s, C_{Ar}), 172.5 (s, C=O), 177.98 (s, C=O). $C_{17}H_{14}N_2O_3Cl$ (365.2). Calcd. C 55.90, H 3.86, N 7.67; found C 55.77, H 3.98, N 7.86.

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