Δ²-1,2-Diazetines: Regioselective Acylation Reactions and Rearrangement into 4H-1,3,4-Oxadiazines

J. Fleischhauer, R. Beckert, J. Weston, M. Schmidt, H.-J. Flammersheim, H. Görls

a Institute of Organic and Macromolecular Chemistry, Friedrich Schiller University, Humboldtstraße 10, 07743 Jena, Germany
b Institute of Physical Chemistry, Friedrich Schiller University, Lessingstraße 8, 07743 Jena, Germany
c Institute of Inorganic and Analytical Chemistry, Friedrich Schiller University, Lessingstraße 8, 07743 Jena, Germany
Fax +49(3641)6948212; E-mail: Rainer.Beckert@uni-jena.de

Received 18 July 2005; revised 17 August 2005

Abstract: Reaction of a 1-substituted Δ²-1,2-diazetine with acid chlorides or anhydrides resulted in the derivatives 3a,b,f that have been acylated at a ring position. On the other hand, trifluoroacetic anhydride yields a new 1,3,4-oxadiazine under the same conditions. The structure of 4e could be confirmed by X-ray structural analysis. Acylated 1,2-diazetidines of type 3a,b can be nearly quantitatively transformed into 1,3,4-oxadiazines 4a,b by thermally induced ring-expansion reactions. Differential scanning calorimetry measurements provide evidence for a monomolecular mechanism in which a strong dependence of the acyl group on the rate of reaction is observed.

Key words: acylations, ring expansion, regioselectivity, heterocycles, imines

Four-ring heterocycles that bear two nitrogen atoms in the ring positions 1 and 2 are quite rare, with only a few examples having been reported in the literature.¹ We have recently developed a procedure for synthesizing Δ²-1,2-diazetidines which possess structural elements of cyclic amidines and amidrazones.² These compounds can also be classified as diazadienes, which may possibly be of value as ligands in metallocomplex chemistry. The nitrogen heteroatoms in these ring systems allow facile acylations. In addition, the inherent ring strain guarantees that such four-ring heterocycles are potential and possibly quite versatile building blocks for ring transformation reactions. Very recently, we could demonstrate that 1,2-diazetines undergo a ring transformation upon reaction with isothiocyanates to yield 1,3,4-thiadiazines.³ Rearrangements involving group transfer reactions in amidines has been a growing area of research in the past two decades.⁴ Acyl groups in amidine derivatives often undergo 1,3-displacement reactions under much milder conditions than those needed to effect the transfer of alkyl or aryl groups. Ring-expansion reactions upon acylation of four-membered heterocycles such as our recently developed 1,2-diazetidines will hopefully extend the number of available cycloamidines available to researchers working in this field.

Treatment of 1,2-diazetines 1 with acyl chlorides or anhydrides 2 in the presence of catalytic amounts of DMAP yields acylated 1,2-diazetidines of type 3 (Scheme 1). This acylation is quite fast and can easily be monitored by TLC.

Although an exocyclic NH proton has been detected in solid-state structures of the starting material,⁵ the ring nitrogen has been regioselectively acylated. DFT calculations [B3LYP/-6-31+G(d,p)] support these experimental findings in that the ring acylated product is ca. 9 kcal/mol more stable than the exocyclic product.⁶

The stability of the acylated diazctetidine depends strongly upon the nature of the substituent R in the acylation reagent 2a–f employed. If R is a relatively soft electron-accepting substituent such as acetyl (2a) or pivaloyl (2b), the acylated diazetidines 3a,b can be isolated in quite good yields. These compounds show an absorption band at 375 nm in their UV/Vis spectra, which is characteristic for s-cis diazadienes. The newly introduced carbonyl group is easily detected in routine IR (1670 cm⁻¹, C=O) and ¹³C NMR (δ = 170 ppm, C=O) spectra. The ¹H NMR spectra of the acyl derivatives 3a,b indicate the presence of dynamic processes at room temperature (probably E/Z-interconversions and/or hindered rotations) since broadened signals for the tolyl and N-methyl protons are ob-

SYNTHESIS 2006, No. 3, pp 0514–0518
Advanced online publication: 11.01.2006
DOI: 10.1055/s-2006-926272; Art ID: Z14305SS
© Georg Thieme Verlag Stuttgart · New York
served. Final and unambiguous proof for the regioselectivity of this acylation was obtained by an X-ray structural analysis of 3a, which is illustrated in Figure 1.

The acetyl and N-methyl group are in a trans-arrangement and the ring is almost planar and, due to quite similar C–C and N–N bond lengths, almost quadratic. The tolyl substituents are twisted slightly (ca. 5°) out of the ring plane. The amide resonance helps to determine the ring planarity. As a consequence, the N2–C4 bond is shorter and the C4–O1 bond somewhat longer than expected.

Treatment of 1 with trifluoroacetic anhydride (2e) yielded a derivative 4e, which could be isolated in a nearly quantitative yield. Although elemental analysis and MS spectra indicated a formal 1:1 composition, the 1H NMR spectrum did not support the formation of an acylation product of type 3. No signal for the carbonyl carbon could be detected (3a: δ = 170 ppm, for example) and the N-methyl signals had been shifted downfield from 2.84 (3a) to 3.53 ppm. A single crystal X-ray structure analysis identified 4e as being a six-membered 1,3,4-oxadiazine heterocycle (Figure 2). The general structure of 4e is quite similar to the related 1,3,4-thiadiazines3 although the ring is quite a bit more symmetrical due to the smaller atomic radius of oxygen as compared to sulfur. The bond angles in the ring vary between 115° and 125°.

Instead of the typical acylation (observed for the acetyl derivative 3a, for example), trifluoroacetic anhydride (2e) had reacted via a ring transformation reaction. This unusual finding prompted us to perform further investigations in this area since 1,3,4-oxadiazines exhibit interesting biological properties. In addition, they have been employed as intermediates in synthetic chemistry as well as chiral auxiliaries for stereoselective reactions.7 However, 1,3,4-oxadiazines which possess an additional vicinal 1,4-diimine substructure (like 4e) are quite rare with only a few having been reported in the chemical literature. For example, a ring-fused 4H-1,3,4-oxadiazine8 could be isolated via a condensation reaction of N'-phenylbenzhydrazide with 2,3-dichloroquinoxaline. 4H-1,3,4-Oxadiazines have also been synthesized in the course of a cycloacylation reaction starting from hydrazine substituted quinoxaline-4-oxides.9

In order to try to expand the palette of available 1,3,4-oxadiazines, we attempted to induce a ring-expansion reaction by heating the acylated diazetidines 3a,b in xylene for two hours at 110 °C. In this manner, the oxadiazines 4a,b were easily obtained in nearly quantitative yields. A solid state structure (X-ray analysis) showing the typical structure of these 4H-1,3,4-oxadiazines (4a) is illustrated in Figure 3. Oxadiazines of type 4 are generally pale yellow and can be clearly distinguished from the diazetidines 3 by a typical hypsochromic shift of about 60 nm in the long-wavelength absorption in UV/Vis spectra.

First mechanistic investigations on this interesting ring expansion reaction 3 → 4 using differential scanning calorimetry (DSC) experiments provide evidence for a slightly exothermic first order phase change – facts which support the assumption of an intramolecular reaction.

A clear tendency is revealed by our initial mechanistic investigations. Four-membered ring systems 3 derived from weak acylation reagents such as the carboxylic acid derivative 2f are quite stable and do not readily undergo a ring expansion reaction to generate an oxadiazine of type 4 – even at higher temperatures. Only traces of the rearranged product can be detected (TLC/MS). If the acceptor char-

Figure 1  Solid-state structure (X-ray analysis) of derivative 3a

Figure 2  Solid-state structure (X-ray analysis) of derivate 4e

Figure 3  Solid-state structure (X-ray analysis) of the 1,3,4-oxadiazine 4a
acter of the acyl substituent in 2 is increased, this destabilizes the acylated diazetidine 3, which then promotes the ring expansion reaction. For example, transforming the acyl derivative 3a into the corresponding oxadiazine 4a requires a much higher temperature (ca. 120 °C) than transforming the 4-chlorobenzoyl derivative 3e into 4c. This rearrangement takes place at room temperature; albeit rather slowly. In the case of the really good acceptor substituent in trifluoroacetic anhydride, the four-ring derivative 3e can neither be isolated nor detected. Rearrangement into the thermodynamically more stable oxadiazine 4e occurs immediately (Scheme 1).

This type of ring transformation is quite rare, having been reported only for one example in the chemical literature. Taylor and co-workers reported that 2-acylated 1-(diphenylmethyl)-1,2-diazeti-dines-3-ones undergo a ring expansion to give 1,3,4-oxadiazin-6-ones in excellent yields.10 We are now working on expanding the range of this ring transformation in addition to performing extensive mechanistic investigations of both experimental and theoretical nature and will be reporting our results in a forthcoming article.

All solvents were dried and purified by standard techniques. The reagents employed were of commercial quality (Aldrich, Lancaster, Fluka, Merck). Reactions were monitored by TLC using aluminum plates coated with Al2O3 from Fluka. Melting points were measured with a B-545 (Boetius system) from Büchi, and are uncorrected. All solvents were dried and purified by standard techniques. The reactant gases were obtained from Fisons. Elemental analyses were carried out with an automatic analyzer Varion EL III from Elementar Analysensysteme GmbH.

Crystal Structure Determination

The intensity data for the compounds were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo-Kα radiation. Data were corrected for Lorentz and polarization effects, and for absorption effects.11,12 The structures were solved by direct methods (SHELXS13) and refined by full-matrix least squares techniques against Fo2 (SHELXL-97).14 All hydrogen atoms were included at calculated positions with fixed thermal parameters. All nonhydrogen atoms were refined anisotropically.14 XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

Ring-Acylation (and Following Ring-Transformation) of 1 to give Acylated 1,2-Diazetidines 3a,b,f and 1,3,4-Oxadiazines 4c,e; General Procedure

A solution of THF (25 mL), Et3N (0.4 mL, 2.5 mmol) and DMAP (20 mg, 0.2 mmol) was cooled to –78 °C and a solution of the corresponding acylation reagent 2 (2 mmol) in THF (5 mL) was slowly added. Afterwards, a solution of the Δ2,1-1,2-diazenone 1 (556 mg, 2 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm up to 0 °C under stirring for 2 h. The solvent was then removed in vacuo and the residue was purified by column chromatography (Al2O3, toluene) and recrystallization from heptane.

Thermally-Induced Ring-Transformation of 1 into 1,3,4-Oxadiazines 4a,b; General Procedure

A solution of xylene (25 mL) and the Δ2-1,2 diazine 1 (556 mg, 2 mmol) was heated under stirring to 120 °C for 2 h. The solvent was removed in vacuo and the residue was purified by recrystallization from heptane.

1-Acetyl-2-methyl-3,4-bis(4-tolylamino)-1,2-diazetidine (3a)

Yield: 85%; yellow crystals; mp 94.5 °C.

IR (ATR): 1688 cm–1 (C=O).

1H NMR (250 MHz, THF-d8): δ = 7.59–6.26 (m, 8 H, Ar), 2.84 (s, 3 H, CH3N), 2.42 (s, 3 H, CH3), 2.31 (s, 3 H, CH3), 2.18 (s, 3 H, CH3).

13C NMR (63 MHz, THF-d8): δ = 164.75 (C=O), 150.07, 141.74, 139.67, 134.97, 134.60, 133.48, 127.49, 127.10, 122.65, 120.30, 36.63 (CH2, N), 20.10 (CH3), 18.32, 18.18 (CH3).

MS (DEI): m/z = 320 [M]+, 203, 161, 146, 118, 91, 43.


Crystal Data for 3a6

C19H20N4O, Mr = 320.39 g mol–1, yellow prism, size 0.08 × 0.08 × 0.06 mm3, triclinic, space group P–1, a = 7.6472(5), b = 11.0061(5), c = 11.8893(7) Å, α = 117.555(5), β = 94.733(3), γ = 101.59(3)°. V = 851.15(6) Å3. θmax = –90 °C. Z = 2, ρcalc = 1.250 g cm–3, μ (Mo-Kα) = 0.8 cm–1, F(000) = 340, 5976 reflections in h–9/8, k–13/14, l–15/14, measured in the range 2.10° ≤ θ ≤ 0 to 27.42°, completeness θmax = 99.5%, 3861 independent reflections, Rint = 0.033, 2444 reflections with Fc > 4σ(Fc), 217 parameters, 0 restraints, R1 = 0.062, wR2 = 0.146, R1 = 0.107, wR2 = 0.174, GoOF = 1.025, largest difference peak and hole: 0.361–0.291 e Å–3.

Selected Bond Lengths and Angles

O(1)–C(4) 1.216 (3), N(1)–C(3) 1.468 (3), N(2)–C(4) 1.378 (3), N(3)–C(1) 1.266 (3), N(4)–C(2) 1.258 (3), C(1)–C(2) 1.503 (2). C(1)–N(1)–N(2) 133.2 (2), N(4)–C(2)–N(2) 126.4 (2). C(1)–N(1)–N(2) 126.3 (2), N(4)–C(2)–N(2) 123.8 (2), C(1)–N(1)–N(2) 129.79, 129.67, 129.49, 129.35, 129.8, 130.31, 130.26, 130.26, 129.95, 129.50, 123.12, 40.24 [C(CH3)3], 38.98 (CH2, N), 26.26 [C(CH3)2], 21.19, 21.04 (CH3).


Anal. Calcd for C22H26N4O: C, 72.90; H, 7.23; N, 15.46. Found: C, 72.93; H, 7.16; N, 15.44.

1-Methyl-2-pivaloyl-3,4-bis(4-tolylamino)-1,2-diazetidine (3b)

Yield: 80%; yellow crystals; mp 89.9 °C.

IR (ATR): 1669 cm–1 (C=O).

1H NMR (250 MHz, THF-d8): δ = 7.58–6.25 (m, 8 H, CH2), 2.82 (s, 3 H, CH3N), 2.31 (s, 6 H, CH3), 1.42 [s, 9 H, C(CH3)3].

13C NMR (63 MHz, THF-d8): δ = 175.19 (C=O), 152.09, 143.77, 142.83, 141.59, 137.37, 136.14, 130.33, 129.95, 125.30, 123.12, 40.24 [C(CH3)3], 38.98 (CH2, N), 26.26 [C(CH3)2], 21.19, 21.04 (CH3).

MS (DEI): m/z (%) = 350 [M]+, 261, 233, 205, 146, 118, 43.
Anal. Calcd for C_{19}H_{17}F_{3}N_{4}O: C, 61.19; H, 4.50; N, 15.01. Found: C, 61.19; H, 4.61; N, 14.93.

N(4)–C(3)–O(1) 122.11 (15), N(4)–C(3)–C(2) 121.43 (15), O(1)–C(3)–C(2) 116.46 (14).

Acknowledgment

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 436).

References


(6) CCDC 277992 (3a), 277993 (4a) and 277994 (4e) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336 033; or deposit@ccdc.cam.ac.uk).


