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Tetrahedron Letters 45 (2004) 4371–4374
Tetrahedron Letters

Acid catalysed methanolysis of 2,5-diazabicyclo[2.2.2]octane-3,6-diones: scope and limitations

Bie M. P. Verbist, Wim J. Smets, Wim M. De Borggraeve, Frans Compernolle and Georges J. Hoornaert*

Laboratorium voor Organische Synthese, K.U. Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

Received 11 March 2004; revised 29 March 2004; accepted 30 March 2004

Abstract—The selective methanolysis of 2,5-diazabicyclo[2.2.2]octane-3,6-dione systems is a key step in a synthetic procedure leading to 4-amino-6-oxo-2-piperidinecarboxylate systems. This reaction seems to be primarily governed by steric hindrance caused by the substituents at the 1- and 4-bridgehead positions of the dione. In absence of bulky substituents the methanolysis is directed by the secondary or tertiary nature of the two lactam moieties.

1. Introduction

In our previous work a synthetic strategy has been developed, which led to 4-amino-6-oxo-2-piperidinecarboxylate (APC) systems that can be used as β-turn mimics.[1] A key step in this procedure is the selective acid catalysed methanolysis of a secondary lactam function in the presence of a tertiary one.[2] This behaviour is in agreement with the general observation that the rate-controlling step during acid hydrolysis of amides is the attack of water on the *O*-protonated amide to form a tetrahedral intermediate: indeed, steric retardation of the latter process appears to be the governing factor in many cases.[3]

However, an anomalous behaviour was observed for simple secondary and tertiary *N*-methylamides since the latter react slightly faster upon acid hydrolysis.[3] This result is probably due to nonsteric factors, for example, σ-donation by the *N*-alkyl substituents and/or solvation effects. Some other examples of the selective acidic cleavage of a tertiary lactam over a secondary one have been reported for nonrelated bislactam systems, that is a strained bridged bislactam,[4] and a 7/5 ring-fused structure.[5]

In order to check the generality of our approach we performed a more profound study of the factors governing the feasibility and the selectivity of the methanolysis of 2,5-diazabicyclo[2.2.2]octane-3,6-dione systems. The role of bulky substituents at the bridgehead positions 1 and 4 of the dione on the selectivity of the methanolysis as well as the effect of the secondary or tertiary nature of the lactam moiety is disclosed by using 2D NMR analysis, which is found to be a most helpful tool for the structural assignment of the reaction products.

2. Preparation of starting materials

Our approach to the 2,5-diazabicyclo[2.2.2]octane-3,6-dione bicyclic system is based on the pyrazinone chemistry previously developed in our laboratory (Scheme 1).[6] Pyrazinones **1** were synthesised starting from the appropriate aminonitriles and oxalyl chloride. The chlorine atom at the 3-position was substituted by an alkyl group by reacting **1** with 1.2 equiv of the corresponding alkylMgBr in THF at −78 °C. After workup at low temperature and extraction with dichloromethane, products **2** were purified by column chromatography (silica gel, gradient $CH_2Cl_2 \rightarrow EtOAc/CH_2Cl_2$ 2/98). The bicyclic system was generated by a Diels–Alder reaction of ethene on substituted pyrazinones **2** in toluene (steel bomb, 33 atm, 135 °C, 18 h). The crude imidoyl chlorides **3** were converted into **4** by exposure to air moisture (stirring in $CHCl_3$ in an open flask). Evaporation of this reaction mixture and column chromatography yielded the pure diazabicyclooctanediones **4** to be studied.

Keywords: Pyrazinone; Bislactam; Methanolysis; Steric hindrance.
* Corresponding author. Tel.: +32-16-327409; fax: +32-16-327990; e-mail: Georges.Hoornaert@chem.kuleuven.ac.be

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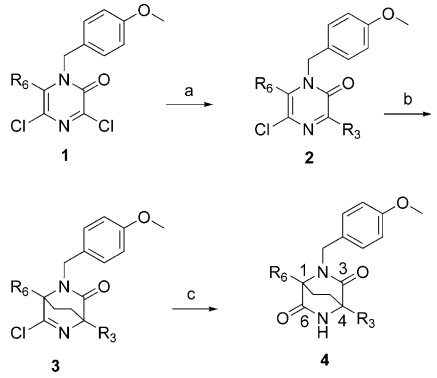
doi:10.1016/j.tetlet.2004.03.186



	1	2	3
R_6=Me/R_3=*i*-Pr	57%	68%	52%
R_6=*i*-Pr/R_3=Me	85%	45%	56%
R_6=Me/R_3=Me	57%	89%	64%

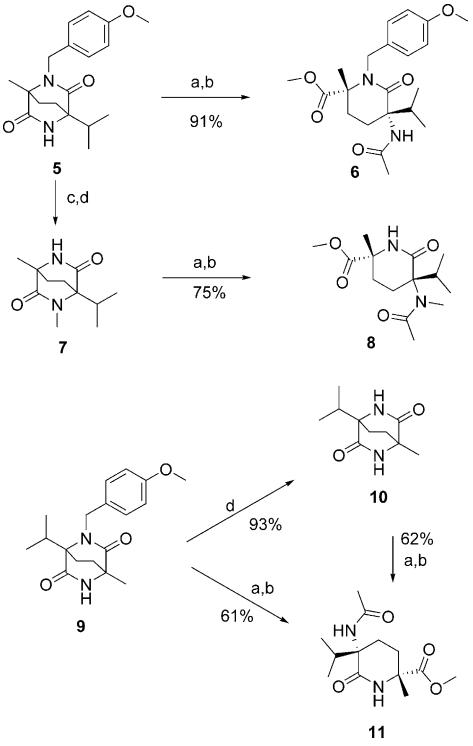
Scheme 1. Synthesis of 2,5-diazabicyclo[2.2.2]octane-3,6-diones. Reagents and conditions: (a) R_3MgBr, THF, −78 °C; (b) ethene, 33 atm, toluene, 135 °C; (c) $CHCl_3$, air moisture, rt.

3. Effect of bulky groups on methanolysis process

Firstly we studied the effect of bulky substituents on the bridgehead positions 1 and 4 of the diones (Scheme 2). Thus treatment of 4-isopropyl-2,5-diazabyclo-[2.2.2]octane-3,6-dione **5** with a HCl-saturated methanol solution overnight resulted in a selective cleavage of the secondary lactam moiety. In order to prevent recyclisation upon neutralisation of the reaction mixture, the newly formed primary amine was trapped as the *N*-substituted acetamide by addition of triethylamine and acetic anhydride. The ammonium salts were removed by filtration and the reaction mixture was evaporated to yield product **6**, which was further purified by column chromatography (silica gel, MeOH/CH_2Cl_2 5/95).

In a second experiment the secondary and tertiary amide functions were interchanged. To this end the secondary amide of bislactam **5** was methylated (NaH, DMF, MeI) and the *para*-methoxybenzyl group was removed by treatment of the purified product (silica gel, CH_2Cl_2/EtOAc 60/40), dissolved in acetonitrile, with 3 equiv of cerium ammonium nitrate (CAN, dissolved in water); this resulted in precipitation of the 2-*N*-deprotected bislactam **7**. The latter was subjected to the acid methanolysis/*N*-acetylation sequence, which now led to selective cleavage of the tertiary amide affording the APC system **8**. The 4-isopropyl group appears to shield the 'top' (2,3) lactam function irrespective of its secondary or tertiary nature. Hence, relief of the bicyclic strain can be attained only by attack of methanol at the sterically more accessible lactam carbonyl group.

This statement also holds for the methanolysis of precursor **10**, obtained after removal of the *p*-methoxybenzyl group by the CAN procedure. In this case the 6-carbonyl function is shielded by the isopropyl group in positon 1 resulting in selective cleavage of the 'upper'

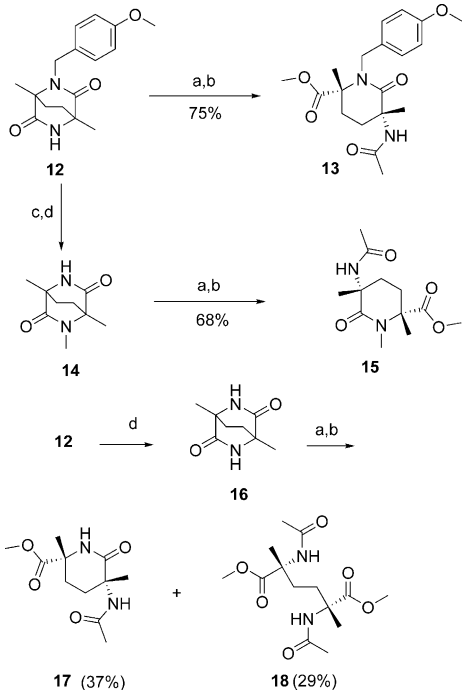


Scheme 2. Effect of bulky substituents on the methanolysis. Reagents and conditions: (a) MeOH, HCl, rt; (b) Ac_2O, Et_3N, rt; (c) NaH, DMF, MeI, rt; (d) CAN, H_2O, 0 °C.

2,3-amide linkage. When precursor **9** is subjected to acid methanolysis compound **11** is also readily formed. In our experience the *p*-methoxybenzyl group is not easily removed from a lactam nitrogen; hence the less hindered tertiary lactam probably is cleaved first followed by removal of the benzylic group from the amine formed after cleavage.

4. Effect of secondary or tertiary lactam group on the methanolysis

In a second part we studied the selectivity for methanolysis in the presence of two equal nonbulky substituents in-position, that is two methyl groups (Scheme 3). Acidic methanolysis of the bicyclic system **12** resulted in selective cleavage of the secondary amide to afford the monocyclic lactam **13**. A comparable behaviour was observed for 2-benzyl-1,4-diphenyl-2,5-diazabicyclo[2.2.2]octane-3.6-dione.[2] When the secondary and tertiary amides were interchanged as in compound **14**, again the secondary amide was cleaved selectively to afford **15**. Removal of the *p*-methoxybenzyl group from **12** provided compound **16** containing two secondary lactam functions. Subsequent treatment of **16** with HCl-saturated methanol solution for 48 h and trapping of the intermediate amine as the *N*-acetyl derivative furnished the monocyclic secondary lactam **17**. However, when the methanolysis was continued for one week, a mixture of singly cleaved product **17** and doubly cleaved compound **18** was obtained. The absence of bicyclic strain accounts for the much slower second cleavage. These results



Scheme 3. Effect of the secondary and tertiary nature of the lactam moiety. Reagents and conditions: (a) MeOH, HCl, rt; (b) Ac_2O, Et_3N, rt; (c) NaH, DMF, MeI, rt; (d) CAN, H_2O, 0 °C.

indicate that a secondary lactam is cleaved preferentially without risk for a tertiary lactam cleavage if bulky substituents are absent. If a secondary lactam remains a second cleavage might occur if the reaction is left for a longer period of time.[7]

To unravel the reasons for the preferential acidic cleavage of the secondary lactam group in the bridged bislactam compounds, we performed a molecular mechanics model study of the two tetrahedral geminal diol intermediates corresponding to attack of water on either one of the two lactam functions of compound **14**. This study clearly revealed a much higher energy (difference ca. 6–7 kcal/mol) for the geminal diol formed next to the *N*-methyl group as compared to the one formed next to NH. Indeed, since the methyl group is now located on an sp^3 *N*-atom in a tight boat conformation it experiences a severe eclipsing interaction with one neighbouring OH group (Fig. 1).

From our combined results it appears that the preferential cleavages observed for the bislactams studied here can be ascribed to two interrelated effects, that is relief of the bicyclic strain which is modulated by the steric retardation caused by the *N*-alkyl and bridgehead substituents. While the first effect enhances the rate of acid hydrolysis of the bicyclic versus the monocyclic lactams, the latter apparently directs the attack of the nucleophile to the less sterically hindered lactam carbonyl group.

The site of cleavage in the APC systems was determined by 2D NMR spectroscopy using the long range ^{13}C–^{1}H couplings between the carbonyl groups and the neighbouring protons (HMBC). The principle is explained for compound **8**. A coupling is noticed between the carbonyl of the methyl ester and the 2-methyl protons as well as a coupling between the *N*-methyl protons and the acetyl carbonyl group as seen in **8a**. These two couplings are not consistent with structure **8b**, formed by cleavage of the other lactam group (Fig. 2).

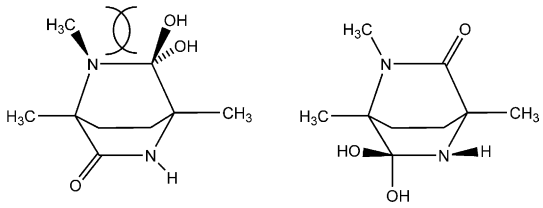


Figure 1. Eclipsing interactions in *gem*-diol intermediates corresponding to hydrolysis at CONMe and CONH groups of **14**.

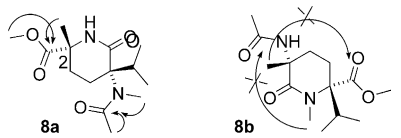


Figure 2. Two possible structures obtained upon methanolysis of compound **7** and structure assignment of **8a** by HMBC.

5. Conclusion

The selective methanolysis of 2,5-diazabicyclo-[2.2.2]octane-3,6-dione systems is a key step in the synthesis of APC type β-turn mimics. A systematic analysis of the factors governing the feasibility and the selectivity of this methanolysis reaction was performed. The main driving force of the reaction is alleviation of the bicyclic strain, which enhances the rate of acid hydrolysis of the bicyclic lactam relative to subsequent cleavage of the monocyclic lactam formed. The selectivity of the methanolysis reaction further depends on the steric factors involving the *N*-alkyl and bridgehead substituents. An isopropyl group at the α-position of the lactam carbonyl seems to prevent completely its sensitivity to methanolysis. In this case, the bicyclic strain will be relieved by cleaving the other lactam function, irrespective of its secondary or tertiary lactam nature. In the absence of bulky α-substituents, secondary lactam functions cleave more readily than tertiary ones. When after the first methanolysis a secondary lactam is still present, a second slow cleavage can occur but tertiary lactams seem to be stable.

Based on these observations on the feasibility and outcome of methanolysis, we are currently designing a number of specific APC-systems for peptide incorporation.

Acknowledgements

The authors wish to thank the Institute for the promotion of Innovation through Science and Technology in

Flanders (IWT-Vlaanderen) and the FWO (Fund for Scientific Research Flanders, Belgium) for financial support. We are grateful to R. De Boer for HRMS measurements and to S. Toppet for 2D NMR. BV thanks the IWT and WDB thanks the FWO for the fellowship received.

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