Journal of Molecular Structure 1053 (2013) 115–121

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Beckmann rearrangement of oxime obtained from oleanolic acid. Structure elucidation of the initial oxime

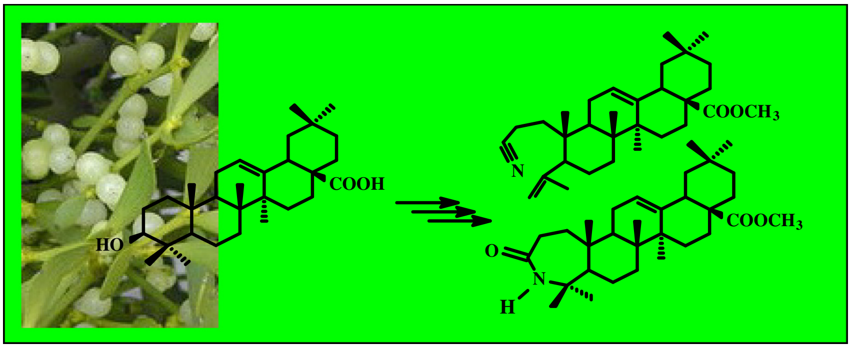
Barbara Bednarczyk-Cwynar *, Lucjusz Zaprutko, Anna Froelich [1]

Department of Organic Chemistry, Faculty of Pharmacy, Poznan University of Medical Sciences, Grunwaldzka Str. No. 6, 60-780 Poznan, Poland

HIGHLIGHTS

- Seven-membered A-lactam and A-nitrile of methyl oleanolate were synthesized from oxime.
- Mechanism of Beckmann rearrangement for oxime of methyl oleanolate was explained.
- The structures of normal and abnormal product were determined and characterized.
- IR, NMR, MS and X-ray data were applied to determine the structure of initial oxime.
- The stereoisomerism of the initial oxime was determined as *E*.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 14 June 2013
Received in revised form 5 September 2013
Accepted 5 September 2013
Available online 11 September 2013

Keywords:
Triterpenes
Oleanolic acid
Azaderivatives of oleanolic acid
Lactams
Beckmann rearrangement

ABSTRACT

Seven-membered A-lactam and A-nitrile of methyl oleanolate were synthesized from the corresponding oxime. Many reaction setups were tried to find the optimum conditions. The best results (the highest yield of the desired lactam along with total consumption of starting oxime) were obtained in pyridine with phosphoryl chloride as Lewis acid. The main product was obtained with the yield of about 60%. Mechanism of Beckmann rearrangement for the above triterpenic 3-oxime leading to normal and abnormal product (a lactam and a nitrile, respectively) was explained. The structures of both products were determined and fully characterized by spectral data. The stereoisomerism of the initial oxime was determined on the basis of Beckmann rearrangement product structure and X-ray analysis.

1. Introduction

Intramolecular amides, so called lactams, are a specific group of compounds that may be obtained as a result of Beckmann rearrangement of a corresponding cyclic oxime in a presence of Lewis acid that serves as an electron pair acceptor. The most commonly used Lewis acids in Beckmann rearrangements are: phosphorus pentachloride, diphosphorus pentoxide, conc. sulfuric acid, alkylsulphonic acid halides (R—SO$_2$—Cl), phosphoryl chloride, formic acid, liquid SO$_2$ and polyphosphoric acid [1]. Recent papers concerning this subject describe the formation of lactams by Beckmann rearrangement performed with less conventional rearrangement agents, e.g.: metaboric acid [2], unchanged zeolites [3,4], rare earth metal ion exchanged zeolites [5], silica supported molybdenum (VI) oxide [5], bismuth (III) triflate [6], Eaton reagent (P$_2$O$_5$—MeSO$_3$H) [6], triphosphazene [7]. Beckmann rearrangement

---

* Corresponding author. Tel.: +48 061 854 66 74; fax: +48 (61) 854 66 80.
E-mail address: bcwynar@ump.edu.pl (B. Bednarczyk-Cwynar).

[1] Current address: Department of Pharmaceutical Technology, Faculty of Pharmacy, Poznan University of Medical Sciences, Grunwaldzka Str. No. 6, 60-780 Poznan, Poland. Tel.: +48 (61) 854 66 55; fax: +48 (61) 854 66 66.

0022-2860/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.molstruc.2013.09.006

can be also performed in supercritical water [8] or in ionic liquids [9].

Several studies concerning Beckmann rearrangement of triterpenic oximes leading to A-nitrile and seven-membered A-lactam are described in the literature. In 1970 Hase [10] presented the synthesis of allobetulin A-nitrile and A-lactam from the corresponding oxime. After the treatment of allobetulone oxime with *p*-toluenesulphonyl chloride in pyridine for one week at room temperature, the nitrile was obtained in 48% yield and the lactam in 37% yield. The reaction performed for two days in the same conditions gave lactam in 81% yield (nitrile yield was unknown) whereas application of *p*-toluenesulphonyl chloride in pyridine at 90 °C only the nitrile was formed (57%).

Askam and Bradley [11] subjected methyl glycyrhhetinate oxime to the action of *p*-toluenesulphonyl chloride in pyridine at room temperature and obtained nitrile with the yield of 14.4% and A-ring lactam in 76% yield. Application of an excess of *p*-toluenesulfonyl chloride under reflux led only to the nitrile (60%). When phosphorus pentachloride in dichloromethane instead of *p*-toluenesulphonyl chloride was used only the lactam was isolated (65%). Refluxing of methyl glycyrrhetinate A-lactam with *p*-toluenesulphonyl chloride gave the nitrile.

Mikhailowa and co-workers [12] obtained methyl glycyrrhetinate A-lactam as a result of treatment of the corresponding oxime with thionyl chloride in dioxane at 10 °C. The main product was isolated in 76% yield. Refluxing of methyl glycyrrhetinate oxime with *p*-toluenesulphonyl chloride in pyridine gave the corresponding nitrile in 70% yield. Gaware et al. [13] treated glycyrrhetinic acid oxime with phosphorus pentachloride in dichloromethane at room temperature. The corresponding A-lactam was obtained in 40% yield, but there is no data whether the accompanying nitrile was present.

Moiteiro and co-workers [14] obtained friedelin A-lactam as a result of treatment of the corresponding oxime with *p*-toluenesulfonyl chloride in refluxed pyridine. After 5 h the friedelin lactam was obtained in quantitative yield.

Beckmann rearrangement performed for 28-norlupeol [15], lupeol [15,16] and dihydrolupeol [16] oximes were also described in the literature. Wahhab and co-workers [15] subjected 28-norlupeol oxime and lupeol oxime to the action of *p*-toluenesulfonyl chloride in pyridine at room temperature to obtain the corresponding nitriles in 67.0% and 57.9% yields, respectively. According to Kumar et al. [16], Beckmann rearrangement of lupeol oxime with 1,1-carbonyldiimidazole (CDI) and allyl bromide in refluxing acetonitrile gave the corresponding lactam while in presence of phosohorous oxychloride in pyridine both lactam and nitrile were obtained. No data concerning the yields of the isolated compounds were presented.

The products of Beckmann rearrangement and Beckmann fragmentation within the ring A of ursolic acid were also described in the literature. These compounds were synthetized by Gnoatto and co-workers [17] from the corresponding oxime upon the action of $SOCl_2$ in THF in 50% and 32% yields, respectively.

Akhmetova et al. [18] obtained an oxime of taraxane. The intensities of the C(3) signals for the *E* and *Z* isomer in the ^{13}C NMR spectra recorded with a long pulse delay indicated that the product of this reaction was in fact a mixture of isomeric *E*- and *Z*-oxime in the ratio of 2:1. The total yield was 89%. Beckmann rearrangement performed for the resulting isomeric mixture was unsuccessful in the presence of *p*-toluenesulfonyl chloride, whereas the similar reaction in the presence of thionyl chloride in dioxane gave A-nitrile as a 1:2 mixture of (2*R*)- and (2*S*)-stereoisomers (total yield of isomers: 84%). The determination of the isomeric nitriles ratio was based on the intensities of the C(13) and C(14) signals in the ^{13}C NMR spectrum.

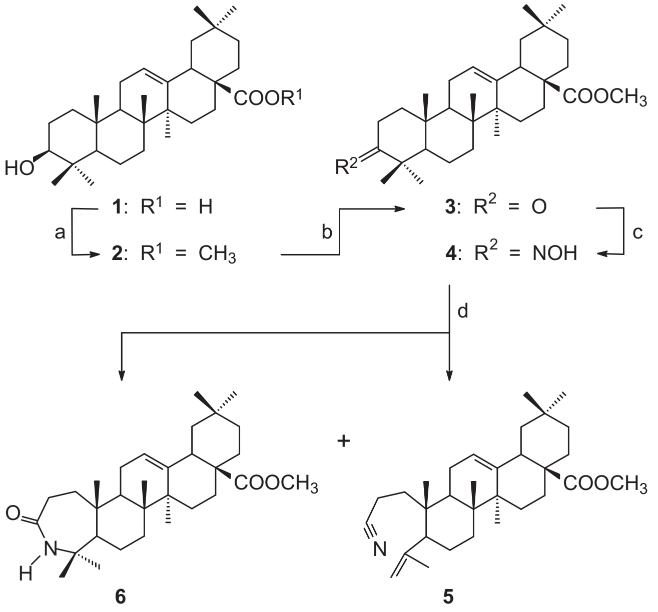
Compounds with seven-membered heterocyclic ring A are not extensively investigated among oleanolic acid derivatives. First synthesis of seven-membered A-lactam of oleanolic acid was published in 1971 by Wrzeciono and co-workers [19]. Oxime of oleanolic acid was treated with tosyl chloride in pyridine as a rearrangement activator at 100 °C for 3 h and two main products were isolated. The less polar compound was obtained in 24% yield and identified as a nitrile derivative with cleaved ring A, while the second product was isolated in 32% yield and identified as lactam derivative with seven-membered heterocyclic ring A. Sundararamaiah with co-workers [20] obtained the same products by heating the starting oxime to 130 °C in pyridine with phosphoryl chloride as a rearrangement agent. After the chromatography, nitrile and lactam were obtained with a yield of 12% and 40%, respectively.

Another seven-membered A-lactam derivative of oleanolic acid was obtained in 1974 by Yasue and co-workers [21]. In this experiment oxime of oleanolic acid morpholide was subjected to Beckmann rearrangement in pyridine using tosyl chloride as a rearrangement activator at room temperature. The new compounds contained two nitrogen atoms, one within the morpholide function, and the other one within the lactam system or nitrile function. The nitrile was obtained in 74% yield, but the yield of lactam was unknown.

2. Results and discussion

The initial compound in our experiments, oleanolic acid (**1**), was isolated from by-product residue obtained during the industrial production of mistletoe (*Viscum album*) extract. The purity of the obtained triterpene was proved on the basis of spectral data which were in accordance with the literature [22]. The further transformations of the mentioned triterpene are presented in Scheme 1.

Carboxyl group of oleanolic acid (**1**) was methylated with dimethyl sulfate. The spectral data of the obtained product (**2**) were also in agreement with the literature data [23]. The C-3 hydroxyl group of **2** was subsequently oxidized with Jones reagent (Scheme 1) in acetone at room temperature [24]. The resulting ketone **3** in the next step was heated in the presence of



Scheme 1. Synthesis of nitrile **5** and lactam **6**. Reactions and conditions: (a) $(CH_3)_2SO_4$, NaOH, C_2H_5OH, reflux; 96%; (b) Jones reagent, acetone, rt.; 90%; (c) $NH_2OH \times HCl$, C_2H_5OH, reflux; 93%; (d) $POCl_3$, pyridine, rt; 25% (for 5); 56% (for 6).