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STABLE HYDRATE OF A β-LACTAMCARBALDEHYDE

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ABSTRACT. Structural features of a stable aldehyde hydrate without a proximal electron withdrawing group are described. The title β-lactamcarbaldehyde has been prepared by hydrolysis of the corresponding imine and characterized by 2D NMR spectroscopy, thermogravimetry and chemical reactions.

Keywords: *aldehyde hydrates, β-lactams, geminal diols, 2D NMR, thermogravimetry*

In memoriam Dr. József Nyitrai,
late professor of the Department of Organic Chemistry and Technology, deceased August 2011.

INTRODUCTION

Compounds with a β-lactam skeleton are known to possess antibacterial and/or β-lactamase inhibitory activity. In the course of our program of the synthesis of new compounds with condensed β-lactam skeleton, 2,3-cis-4-oxo-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-carb-aldehyde (**1**) was needed.

According to the literature this aldehyde is available by oxidative methods only i.e. oxidation of i) 3,4-*cis*-1-(4-methoxyphenyl)-3-phthalimido-4-propenylazetidin-2-one[1], or of 3,4-*cis*-1-(4-methoxyphenyl)-4-(2-phenyl-ethenyl)-3-phthalimidoazetidin-2-one with ozone[2]; ii) oxidation of 3,4-*cis*-4-(1,2-dihydroxyethyl)-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-one with sodium

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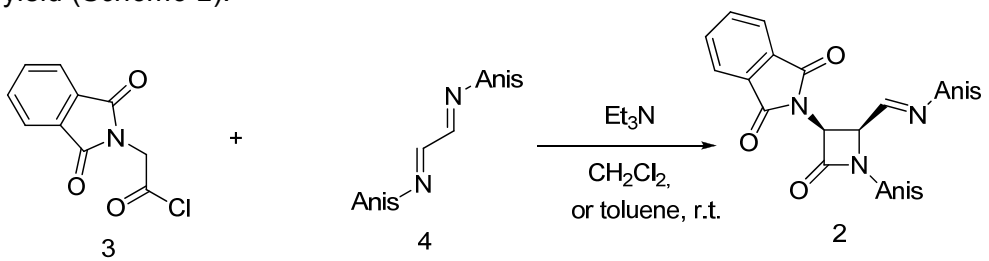
periodate[3], and oxidation of 3,4-*cis*-4-(hydroxymethyl)-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-one[4], followed by *in situ* acidic hydrolysis of 3,4-*cis*-1-(4-methoxyphenyl)-4-[(4-methoxyphenyl)-imino-methyl]-3-phthalimidoazetidin-2-one (**2**) in a two phase system[3,5]. In our hands, however, acidic hydrolysis of 3,4-*cis*-1-(4-methoxyphenyl)-4-[(4-methoxyphenyl)-iminomethyl]-3-phthalimidoazetidin-2-one (**2**) in homogenous water–DMF phase resulted in the formation of a novel compound lacking an aldehyde function. In this communication the structural features of this compound are described.

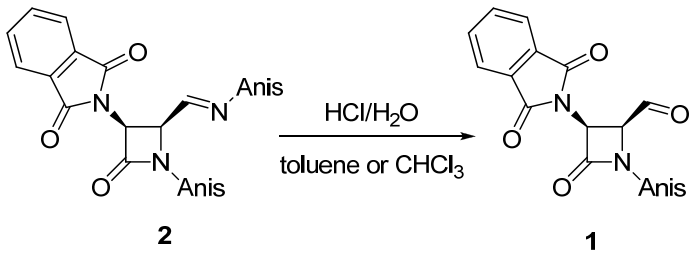
RESULTS AND DISCUSSION

The starting material, 3,4-*cis*-1-(4-methoxyphenyl)-4-[(4-methoxyphenyl)imino-methyl]-3-phthalimidoazetidin-2-one (**2**) was obtained by Staudinger reaction of *N*,*N*'-(ethane-1,2-diylidene)bis(4-methoxyaniline) (**3**) and phthalimidoacetyl chloride (**4**) (*Scheme 1*; Note that all β-lactams described in this paper are racemic and only one enantiomer is shown).

Previously Grigg *et al*.[3], and Alcaide *et al*.[5] conducted the same Staudinger reaction but in toluene, followed, without isolation of the imine **2**, by hydrolysis in a two phase system to give 2,3-*cis*-4-oxo-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-carbaldehyde (**1**) from the organic phase in moderate yield (*Scheme 2*).

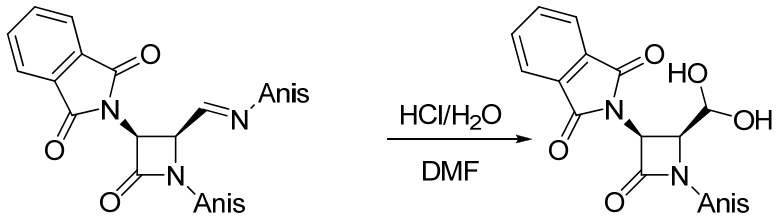


Scheme 1. *Staudinger reaction yielding β-lactam imine* ***2*** *from bisimine* ***4*** *and acid chloride* ***3***



Scheme 2. *Deprotection of β-lactam imine* ***2*** *to β-lactam carbaldehyde* ***3***

We were surprised to find that, when the hydrolysis of the imine **2** was performed in a homogenous HCl/water/DMF system, the reaction resulted in the formation of a new compound (**5**) (*Scheme 3*).



2 **5**

Scheme 3. *Deprotection of β-lactam imine **2** to β-lactam carbaldehyde hydrate **5***

In the IR spectrum of **5** no carbonyl absorption for a formyl group was observed, while broad absorption bands were present in the OH stretching region. Moreover, characteristic signals for an aldehyde group were absent both in the ^{1}H- and ^{13}C-NMR spectra. Next, besides the normally expected AA'XX' systems of the 4-methoxyphenyl (PMPh) and phthalimido (Phth) units, five additional signals were observed for five hydrogen atoms in the region 4.3–6.6 ppm. Since two of them could be easily assigned to the β-lactam skeleton, the other three had to be attributed to the newly formed functionality. In the ^{13}C-NMR spectra of **5** the sole new signal not related to the 4-methoxyphenyl (PMPh), phthalimido (Phth) or β-lactam units, found at 90.0 ppm, was indicative of the presence of a methine unit bearing two hydroxyl groups.

Finally elemental analysis of **5** was consistent with the molecular formula $C_{19}H_{16}N_2O_6$ with 0.5 mol water of crystallization. ^{1}H NMR signal for the latter was overlapped by the signal of the water content of the solvent.

These results suggested that one of the 4-methoxyphenylimino group indeed hydrolyzed, but subsequent reaction of the resulting aldehyde with water provided a stable hydrate **5** (*Scheme 3*). This unexpected result prompted a more detailed investigation.

Thermal analysis showed in the DTA curve (*Figure 1*) three endothermic peaks. TG results indicated that the first and the second endothermic transformation, at 71 ºC and 135 ºC respectively involved weight loss, of, while the third at 219 ºC belongs to the melting of the sample where after decomposition started The first weight loss, with a maximum at 68 ºC, (see the DTG curve) – terminated at 90.8 ºC (see TG curve) – belongs to the

loss of 0.5 mol/mol of crystallization water. The second weight loss – with a maximum at 132 ºC, (see DTG curve) – finished at 153 ºC (see TG curve), belongs to the exact loss of one mol/mol of water from the geminal diol moiety of **5**. So the β-lactamcarbaldehyde **1** was formed prior to melting, and it was this carbaldehyde which melted between 217–220 ºC. (Lit. value[3] of m.p. for compound **1**: 214–216 °C).

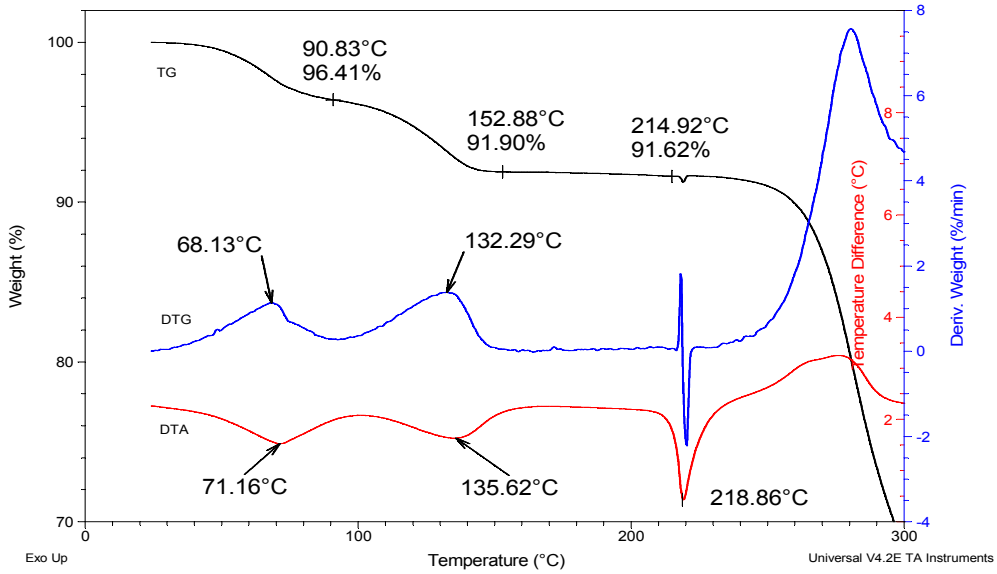


Figure 1. *Thermoanalytical investigation of compound* ***5****:*
TG: top black line, DTG: middle blue line, DTA: bottom red line

The structure of compound **5** was further confirmed by NMR investigations. As a basis for comparison the spectra of compound **2** was examined including APT, HMQC, HMBC, COSY and NOESY experiments.

Thus in the NOESY spectrum of **2** correlation between the C_3-H and C_4-H of the β-lactam skeleton indicated their *cis* arrangement (*Figure 2*).

The *E* configuration of the imine moiety was supported by the correlation between the hydrogen atom of CH=N and the *ortho*-H's of the CH=N–PMPh group (PMPh = 4-methoxyphenyl). The correlation between the C_4-H and the *ortho*-H's of the N_1–PMPh group verified the *trans* arrangement of N_1-PMPh group and C_3-Phth groups.

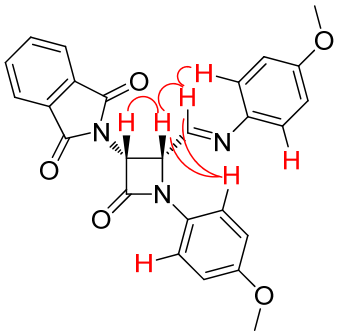


Figure 2. *NOESY investigation of compound* ***2****: Correlations are marked with red arcs*

Relevant $^{1}H–^{13}C$ (hetero) correlations of the signals in the spectra of **5** were supported by APT, HMQC, HMBC, COSY and NOESY methods as well (*Figure 3*).

The sequence $C_3\underline{H}–C_4\underline{H}–C\underline{H}(O\underline{H})_2$ was unambiguously proved by the $^{3}J_{HH}$ scalar couplings observed as follows: i) between β-lactam protons (stereospecific as 6.0 Hz), ii) between C_4-H and the methine-H of the geminal diol moiety (7.7 Hz), and iii) between the methine-H and the diastereotopic OH's of the geminal diol moiety (6.5 Hz in DMSO-d_6 as hydrogen bond acceptor).

In the NOESY spectrum correlation was found between protons C_3-H and C_4-H of the β-lactam skeleton, supporting their *cis* arrangement (*Figure 3*). Correlation between the C_4-H and *ortho*-H's of the N_1–PMPh group verified the *trans* arrangement of N_1-PMPh and C_3-Phth groups.

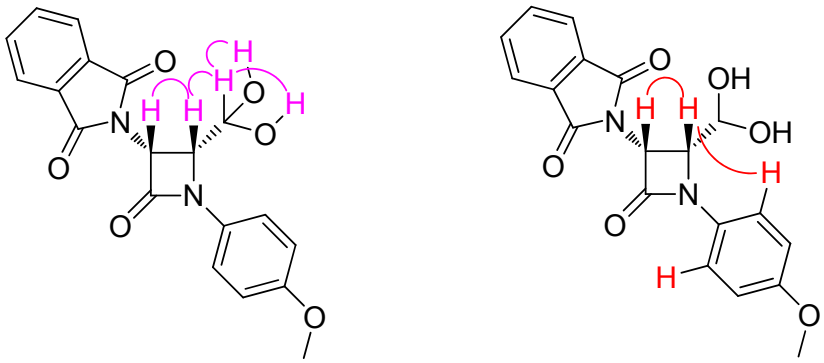
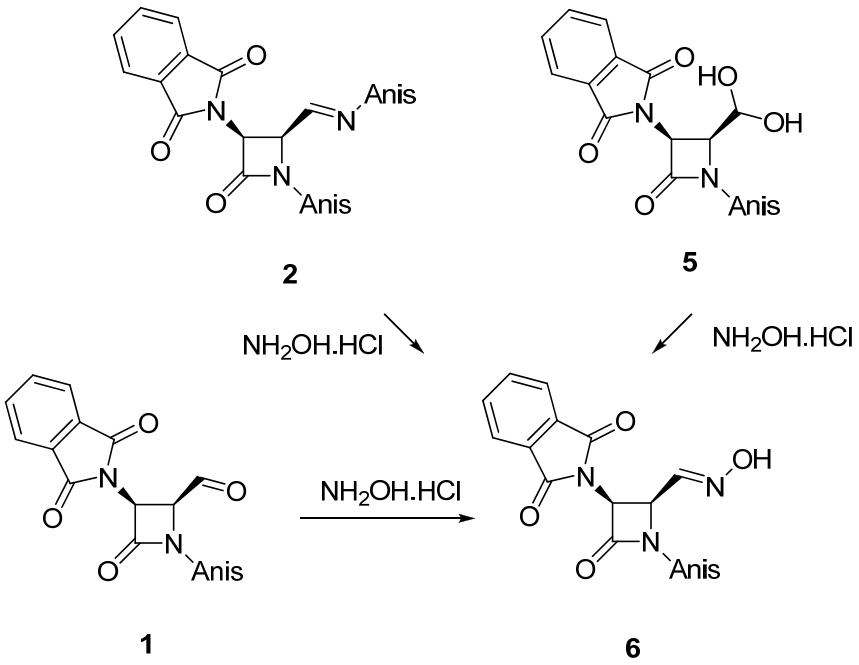


Figure 3. *$^{3}J_{H,H}$ scalar coupling pattern (pink arcs) and NOESY dipolar correlations (red arcs) of compound* ***5***

When the solution of **5** in DMSO-d_6 was stored at room temperature for a week a 3:1 mixture of diol **5** and aldehyde **1** could be detected in the NMR spectra This result proved that slow dehydration of the diol **5** also occurred in a polar but aprotic medium. Note, that the hydrate **5** remained intact during drying its crystals in vacuum at 65 ºC.

The structure of compound **5** was verified also by transforming it to the known aldoxime **6,** previously prepared from the aldehyde **1** [4]. We could prepare this aldoxime **6** not only from the imine **2,** but also from our hydrate **5** (*Scheme 4*).

Aldehyde hydrates (geminal diols) are generally known to be stable only when an electron withdrawing group, such as trichloromethyl in chloral, formyl in glyoxal, or carboxyl in glyoxylic acid, is adjacent to the carbonyl group and but very few examples of aldehyde hydrates stabilized without electron withdrawing effects have been reported. Most of them possess an acylamino group at α- or β-position relative to the geminal diol moiety, *e.g.* 2-(phenylacetylamino)-acetaldehyde hydrate[6], a benzoyl cytidine derivative[7], an α-aminoacid derivative[8], penicillanal hydrate[9], some aminoacid derivatives[10], a triazine derivative[11], and a dimethylglycinal derivative[12].



Scheme 4. *Chemical correlation by formation of aldoxime* ***6***

It has to be noted that in our stable hydrate **5** α-acylamino and β-acylamino units are present adjacent to the geminal diol function. In view of the above examples it can be assumed that hydrates in which no electron withdrawing groups are attached to the parent aldehyde group may be stabilized by hydrogen bonds. We are making efforts to prove this hypothesis.

CONCLUSIONS

Preparation and structural investigations of a stable hydrate **5** of the β-lactamcarbaldehyde **1** are presented. As an extension of existing methods for the preparation of aldehyde **1** we have found, that under aqueous conditions the stable hydrate **5** could be prepared. The dehydrated aldehyde **1** was formed in an organic medium, while the hydrated form **5** arose in a homogenous system containing water. Hydrate **5** was stable in a crystalline form however it was slowly dehydrated on standing in DMSO.

EXPERIMENTAL SECTION

NMR spectra were recorded in $CDCl_3$ or in DMSO-d_6 on a Bruker DRX-500 or on a Bruker DRX-300 spectrometer and are reported in ppm on the δ scale. Infrared spectra were recorded on a Bruker ALPHA FT-IR spectrometer. TLC was carried out on Kieselgel $60F_{254}$ (Merck) sheets. Spots were visualized under UV light (Vilber Lourmat VL-6.LC, 254 nm and 365 nm) or by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates. For thermoanalysis a simultaneous thermogravimetric and differential thermal analysis (TG/DTA) apparatus (STD 2960 Simultaneous DTA-TGA, TA Instruments Inc., USA), a heating rate of 10 °C min^{-1}, an N_2 flow of 130 cm^3/min, sample sizes of ca. 5 mg and open Pt crucibles was used.

3,4-cis-1-(4-Methoxyphenyl)-4-[(E)-(4-methoxyphenyl)iminomethyl]-3-phthalimido-azetidin-2-one (2)

To the solution of *N*,*N*'-(ethane-1,2-diylidene)bis(4-methoxy-aniline) (10.89 g, 40.59 mmol) and triethyl amine (6 mL, 42.86 mmol) in of dichloromethane (100 mL) was added at 0 ºC a solution of phthalimidoacetyl chloride (8.89 g, 39.75 mmol) in of dichloromethane (50 mL) within 10 min. The reaction mixture was stirred for 2 hours at room temperature, and then it was washed with of water (50 mL). The organic layer was dried over $MgSO_4$. After evaporation of the solvent the product was crystallized from methanol (50 mL) at 0 ºC to give 13.46 g (29.56 mmol, 73%) of title compound. $C_{26}H_{21}N_3O_5$ (455.47)

M.p.: 149-150 ºC; *IR* (KBr, cm^{-1}): v 2954, 1787 (Phth), 1749 (β-lactam), 1719 (Phth), 1602, 1514, 1465, 1445, 1387, 1297, 1246, 1208, 1187, 1127, 1031, 83, 727; *^{1}H-NMR* (500 MHz, $CDCl_3$, δ ppm): 3.74 (s, 3H, CH_3O), 3.80 (s, 3H, CH_3O), 5.16 (dd, 1H, *J* = 5.8 Hz, 4-H), 5.86 (d, 1H, *J* = 5.8 Hz, 3-H), 6.77 (d, 2H, *J* = 8.9 Hz, =*N*-PMPh), 6.91 (d, 2H, *J* = 8.9 Hz, 1-PMPh), 6.95 (d, 2H, *J* = 8.9 Hz, *N*-PMPh), 7.46 (d, 2H, *J* = 8.9 Hz, 1-PMPh), 7.73 (m, 2H, Phth), 7.84 (m, 2H, Phth), 8.09 (d, 1H, *J* = 5.8 Hz, CH=N); *^{13}C-NMR* (125 MHz, $CDCl_3$, δ ppm): 55.30 (CH_3O), 55.39 (CH_3O), 56.49 (C_3), 60.92 (C_4); 114.17, 114.52, 118.14, 122.06 (PMPh-CH's); 123.71 (Phth-CH), 130.85 (PMPh-C_1), 131.33 (Phth-C), 134.53 (Phth-CH), 142.70 (PMPh-C_1), 156.61 (PMPh-C_4), 156.98 (C=N), 158.83 (PMPh-C_4), 160.54 (C_2), 166.95 (Phth-CO).

3,4-cis-4-(Dihydroxymethyl)-1-(4-methoxyphenyl)-3-phthalimido-azetidin-2-one (5)

3,4-*cis*-1-(4-Methoxyphenyl)-4-[(4-methoxyphenyl)iminomethyl]-3-phthalimidoazetidin-2-one (**2**) (455 mg, 1.00 mmol) was dissolved in DMF (12 mL) then 1M hydrochloric acid (2 mL) was added in one portion. The reaction mixture was stirred at room temperature for 1.5 hours, and then water (36 mL) was added with stirring, while a precipitate was formed. The precipitate was filtered off, washed with water, methanol and diethyl ether. The white powder was dried in vacuum at 65 ºC to give 305 mg (0.808 mmol, 81%) **5** as crystals containing 0.5 mol of crystal water. *Anal.*: $C_{19}H_{16}N_2O_6$*0.5 H_2O (377.36) Calc.: C 60.48, H 4.54, N 7.42 %, found: C 60.52, H 4.52, N 7.13 %;

M.p.: 217-220 ºC. *IR* (KBr, v cm^{-1}): 3537, 3387 (br), 1775 (Phth), 1743 (β-lactam), 1704 (Phth), 1516, 1435, 1401, 1301, 1250, 1208, 1181, 1126, 1109, 1074, 1054, 1032, 1020, 731, 712; *^{1}H-NMR* (500 MHz, DMSO-d_6, δ ppm): 3.74 (s, 3H, CH_3O), 4.33 (dd, 1H, *J* = 6.0 Hz, *J* = 7.7 Hz, 4-H), 4.95 (td, 1H, *J* = 6.5 Hz, *J* = 7.7 Hz, C<u>H</u>$(OH)_2$), 5.58 (d, 1H, *J* = 6.0 Hz, 3-H), 6.10 (d, 1H, *J* = 6.5 Hz, OH), 6,49 (d, 1H, *J* = 6.5 Hz, OH), 6.94 (d, 2H, *J* = 8.9 Hz, 1-PMPh), 7.62 (d, 2H, *J* = 8.9 Hz, 1-PMPh), 7.90 (m, 2H, Phth), 7.93 (m, 2H, Phth); *^{13}C-NMR* (125 MHz, DMSO-d_6, δ ppm): 54.34 (C_3), 55.46 (CH_3O), 62.16 (C_4), 89.99 ($CH(OH)_2$), 113.93, 119.61 (PMPh-CH's); 123.66 (Phth-CH), 131.41 (Phth-C), 131.75 (PMPh-C_1), 135.09 (Phth-CH), 155.86 (PMF-C_4), 162.61 (C_2), 167.28 (Phth-CO).

After standing for a week in DMSO-d_6 at room temperature there were two sets of signals in the NMR spectra. Major component: 3,4-*cis*-4-(dihydroxymethyl)-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-one (**5**), minor component: 2,3-*cis*-4-oxo-1-(4-methoxyphenyl)-3-phthalimido-azetidin-2-carbaldehyde (**1**).

NMR data of **1**: *^{1}H-NMR* (500 MHz, DMSO-d_6, δ ppm): 3.77 (s, 3H, CH_3O), 5.18 (d, 1H, *J* = 6.5 Hz, 4-H), 5.97 (d, 1H, *J* = 6.5 Hz, 3-H), 7.01 (d, 2H, *J* = 9.0 Hz, PMPh), 7.49 (d, 2H, *J* = 9.0 Hz, PMPh), 7.90 (m, 2H, Phth), 7.93 (m, 2H, Phth), 9.78 (s, 1H, CHO); ^{13}C-NMR (125 MHz, DMSO-d_6, δ ppm): 55.18 (C_3), 55.55 (CH_3O), 62.34 (C_4), 114.70, 118.31 (PMF-CH's); 124.00 (Phth-CH), 131.02 (Phth-C), 131.06 (PMF-C_1), 135.49 (Phth-CH), 156.32 (PMF-C_4), 161.14 (C_2), 166.90 (Phth-CO), 197.87 (CH=O).

3,4-cis-4-(Hydroxyiminomethyl)-1-(4-methoxyphenyl)-3-phthalimido-azetidin-2-one (6)

Method A: 3,4-*cis*-4-(dihydroxymethyl)-1-(4-methoxyphenyl)-3-phthalimido-azetidin-2-one (**5**) (193 mg, 0.511 mmol) was dissolved in DMF (5 mL) and then hydroxylamine hydrochloride (345 mg, 4.96 mmol) was added. The reaction mixture was stirred for 30 min, d then water (20 mL) was added with stirring, while a precipitate was formed. The precipitate was filtered off, washed with water, methanol and diethyl ether. The white powder was dried in vacuum at room temperature to give 139 mg (74%) of the title compound. $C_{19}H_{15}N_3O_5$ (365.35) M.p.: 234 ºC (lit.: 228-230 ºC [4]).

Method B: 3,4-*cis*-1-(4-methoxyphenyl)-4-[(4-methoxyphenyl)iminomethyl]-3-phthalimidoazetidin-2-one (**2**) (4.60 g, 10.1 mmol) was dissolved in a mixture of methanol (20 mL) and dichloromethane (20 mL), and then hydroxylamine hydrochloride (4.32 g, 62.1 mmol) in water (5 mL) was added. The reaction mixture was stirred for 60 min, and then water (50 mL) was added, and the product was extracted with dichloromethane (2 × 50 mL). The combined organic extract was washed with water, and dried over $MgSO_4$. After evaporation of the solvent the product was crystallized from diethyl ether (20 mL) to give 2.88 g (78%) of title compound.

IR (KBr, v cm^{-1}): 3377 (br), 3312 (br), 1782, 1722, 1514, 1469, 1388, 1301, 1251, 1206, 1191, 1180, 1130, 1102, 1026, 826, 713; *^{1}H-NMR* (300 MHz, DMSO-d_6): two sets of the signals corresponding to the *E* and *Z* oximes were detected (major isomer ca. 72%, minor isomer ca. 28%), δ (major, ppm): 3.76 (s, 3H, CH_3O), 5.51 (dd, 1H, *J* = 5.7 Hz, *J* = 4.2 Hz, 4-H), 5.92 (d, 1H, *J* = 5.7 Hz, 3-H), 6.80 (d, 1H, *J* = 4.2 Hz, CH=N), 7.01 (d, 2H, *J* = 8.7 Hz, PMPh), 7.34 (d, 2H, *J* = 8.7 Hz, PMPh), 7.92 (m, 4H, Phth), 11.34 (s, 1H, NOH), δ (minor): 3.76 (s, 3H, CH_3O), 5.17 (dd, 1H, *J* = 5.7 Hz, *J* = 7.5 Hz, 4-H), 5.86 (d, 1H, *J* = 5.7 Hz, 3-H), 7.01 (d, 2H, *J* = 8.7 Hz, PMPh), 7.30 (d, 1H, *J* = 7.5 Hz, CH=N), 7.34 (d, 2H, *J* = 8.7 Hz, PMPh), 7.92 (m, 4H, Phth), 11.47 (s, 1H, NOH); *^{13}C-NMR* (75 MHz, DMSO-d_6, δ ppm), two sets of the signals were detected: 54.34 (C_3), 55.40 (CH_3O), 56.05 (C_4), 114.68 and 114.78, 117.80 and 117.99, 123.74 and 123.85, 130.57 and 130.82, 130.88 and 130.95, 135.22 and 135.33, 145.14 (CH=N), 156.05, 160.86, 166.79 and 167.00.

ACKNOWLEDGEMENTS

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