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FROM 1-METHYLNAPHTHALENE TO AMINOBENZOYL-2-HYDROXY-1-NAPHTHYL HYDRAZONE

K. Genov[1], D. Nikolova[2]

[1]*Institute of General and Inorganic Chemistry, Bulgarian Academy of Science Bl. 11 Ak.G.Bonchev str. 1113, Sofia, Bulgaria E-mail: kgenov@svr.igic.bas.bg*

[2]*University hospital "St Marina"-Varna, Clinic of infectious diseases, Medical university - Prof. Dr.Paraskev STOJANOV Varna, 55. Marin Drinov str., Varna 9002*

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ABSTRACT

Some agents of non-nucleonic base analogues are 2-hydroxy-naphthaldehyde-hydrazones, which are HIV-1/2 RTIs. This publication is an attempt to present results of the synthesis of aminobenzoyl-2-hydroxy-1-naphthyl-hydrazone, using catalytic oxidation of 1-methylnaphthalene over Ti-Beta zeolite to 2-hydroxy-1-naphthaldehyde and its further transformation to the corresponding hydrazone.

Keywords: Ti-beta, zeolite, H_2O_2, 1-methylnaphthalene, aminobenzoyl-2-hydroxy-1-naphthyl-hydrazone, oxidation in mild condition, reverse transcriptase inhibitor, NNRTI, HAART.

INTRODUCTION

Nowadays around 40 million people worldwide are infected with HIV and only 1.75 million people are receiving antiretroviral treatment [1]. According to this information, practically the High Active Anti-Retroviral Therapy (HAART) is not worldwide reaching. May be the possible reasons for this is the high prise of drugs. HIV-1 is also very mutable and resistance to existing ART medicaments is huge problem for HIV infected patience, having access to HAART. So, it is necessary to find new compounds which have an anti-retro-viral activity. According to the present European and American guidelines of HIV and AIDS treatment [9-11], non-nucleonic analogues of reverse-transcriptase are a recommended first-line therapy. However, one unwanted side effect is the occurrence of cross resistance. One example of this are the N-acyl hydrazones HIV-1 reverse-transcriptase-DNA-polymerase inhibitors (RTIs), described as non- nucleonic analogues of DNA or RNA's (NNRTI), and discussed by M.A. Parniak et al. [2-5]. One dihydroxy-benzoyl-naphthyl hydrazone RNase H inhibitor is aminobenzoyl-2-hydroxy-1-naphthyl-hydrazone (1) (Fig. 1) [5]. This work shows the synthesis of (1), using catalytic oxidation of 1-methylnaphthalene over Ti-Beta zeolite, as a catalyst in oxidation reaction with H_2O_2, to 2-hydroxy-1-naphthaldehyde and its further transformation to the corresponding hydrazone.

EXPERIMENTAL

Step 0. Preparation of catalyst

The Ti-Beta catalyst was synthesized according to the synthesis procedure called "wetness impregna-

tion method" [6]. This method was first published for TS-1 zeolite and we used a modification of this method for syntheses of Ti-Beta samples. The synthesis procedure, involves 4 steps, with the first and second regarding the cogel preparation and the third one dealing with wetness impregnation, and fourth – crystallization. The scheme as described previously in [7] is given below.

Substep 0.1. Acid step, hydrolysis-condensation

Tetraethylorthosilicate (TEOS, Merck, 98 %) is hydrolyzed with 0.05 M HCl (Sigma- Aldrich, 37 %) to a clear solution HCl:TEOS mol ratio = 1:4 (room temperature, 1 h, use of electromagnetic stirrer).

The necessary amount of $Al(NO_3)_3$ x $9(H_2O)$ (Sigma-Aldrich, > 98 %) is dissolved in water and dropped into the mixture at 0°C. $Al(NO_3)_3$: H_2O mass ratio = 1 : 33.

The titanium source - tetraethylorthotitanate (TEOT, Merck, 95 %) is dissolved in dried *i*-propanol (Merck, > 99 %) and dropped slowly during more than 20 min. into the continuously stirred reaction mixture. The temperature is 0°C. The *i* propanol:TEOT mass ratio reaches 15:1, TEOT:TEOS ratios are calculated in order to obtain the desired Ti:Si ratios in the zeolite sample. The solution is left for ca. 1 h at room temperature to age.

Substep 0.2. Base step, gelation

The final solution of sub-step 0.1. is converted into a solid cogel by drop-wise addition of a template - tetraethylammonium hydroxide (TEAOH, Merck, 20 % aqueous solution), to reach gel point. The resulting cogel is dried overnight at 60°C.

Substep 0.3. Wetness impregnation

The dried cogel is impregnated by addition of the template. Template : cogel ratio = 1 : 2.2

Substep 0.4. Crystallization

The wet solution was put into Teflon autoclaves (Berghof) and crystallized in a conventional oven under autogenous pressure and static condition at 200°C for 7 days. The crystalline product was separated by centrifugation, washed and dried. The yield of the synthesis, defined as amount of Ti-Beta formed with respect to the amount of SiO_2 and TiO_2 present in the amorphous material, was found to be always higher than 95 %. So the Ti-Beta sample obtained, was characterized with methods of XRD, DR-UV-VIS and IR spectroscopy.

For XRD measurements, a Philips PW 1729/ 1050 diffractometer with Cu-Kα radiation were used.

DR-UV-VIS spectra of titanium containing zeolites were recorded on a Varian UV VIS Cary 4 spectrophotometer. In order to optimize the way of the irradiating light, as reference standard (R") $BaSO_4$ (Sigma-Aldrich, purum, p.a.) was used.

The IR spectra in this work were recorded on BIO-RAD FTS-60A IR Spectrophotometer, using KBr (Merck, > 99 %) as mulling agent.

Step 1. Oxidation of 1-methylnaphthalene over Ti-Beta to 2-hydroxy-1-naphth-aldehyde

The reactions were performed with 10 *mL* solvent (*i*-propanol, Merck, > 99 %), 0.3 g catalyst (Ti-Beta), 3 mL substrate (1-methyl-naphthalene, Aldrich, 95 %) and 3 mL oxidant (H_2O_2, Merck, 29.0 - 31.0 % aqueous solution) at the temperature of the boiling point of the solvent (ca. 63°C). The catalytic product mixtures obtained were analyzed on a Merck HPLC instrument equipped with a LiChrosorb RP 18 column and a L-4000 UV-VIS diode array detector. The samples were dissolved in a suitable solvent in a known ratio of 1:10 and filled in 2 mL autosampler flasks. The injector volume was 50 μL. As eluent mixtures of H_2O and methanol (Sigma-Aldrich, CHROMASOLV®, for HPLC, ≥ 99.9 %) in a ratio 70:30 were used.

Step 2. Synthesis of 2 hydroxy-1-naphthylhydrazone

2-hydroxy-1-naphthaldehyde (Aldrich, technical grade), reacts with hydrazine hydrate (H_4N_2 64 % aqueous solution Chimsnab) to hydrazone. The reaction was made for 1 hours in a flask with a stirrer, heating at 50 - 60°C, and as a solvent N, N-dimethylformamide (Sigma, > 99 %) was used. The main product of the reaction - 2 hydroxy-1-naphthylhydrazone was idented with the thin-layer chromatography - Silica gel 60 F_{254} sheets 5x7.5 (Merck), (R_f = 0.69 (hexane:ethyl acetate = 5:1). The hydrazone, was separated from the aldehyde using acid/base extraction, with ethyl acetate as organic phase and water as inorganic phase. After adding of HCl, the hydrazone extracts as hydrochlodire in water phase and dried.

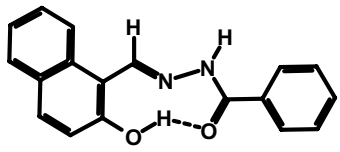

Fig. 1. Aminobenzoyl-2-hydroxy-1-naphthyl-hydrazone (**1**).

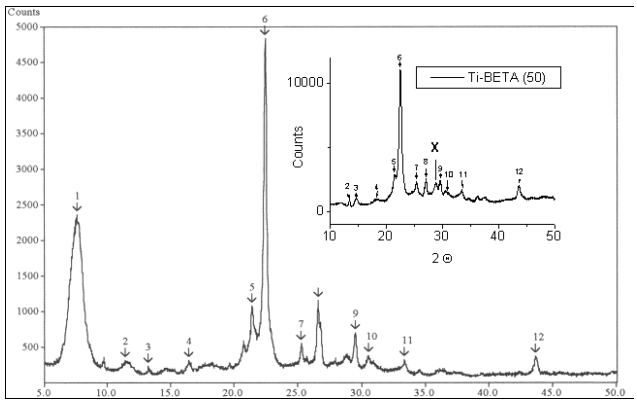

Fig. 2. A XRD pattern of Ti-free Si-Al-Beta [8], and our Ti-Beta.

Step 3. Synthesis of aminobenzoyl-2-hydroxy-1-naphthyl hydrazone (1)

2 hydroxy-1-naphthylhydrazone reacts further with benzaldehyde (Aldrich, > 99 %) to the corresponding azine (1). The reaction was conducted in a flask with stirrer, again under mild conditions and a neutral solvent (DMF, Sigma > 99 %) for 1 hour. The product was analyzed and proved with references on TLC, Silica gel 60 F_{254} sheets 5x7.5 (Merck) (R_f = 0.75 (hexane:ethyl acetate:acetone = 5:1:1) . The product of reaction (**1**) was separated from the reaction mixture again with the acid/base extraction.

RESULTS AND DISCUSSION

Step 0.

As reference a diffractogram of Si-Al-Beta without any other metals given by Serrano et al. [8] and a diffractogram for our catalyst Ti-Beta were used. The Si-Al-Beta diffractogram (Fig. 2) as well as the literature and our Ti-Beta pattern show the same reflections as our sample with very comparable intensities, indicating that we obtained a highly crystalline material.

The UV-VIS spectra of some Ti-Beta (Fig. 3) samples, show a strong band around 210 nm, which can be attributed to a tetracoordinated position of Ti(IV) on zeolite framework. The band originates from the charge transfer of the pπ-dπ transition between titanium and oxygen of the framework Ti-O-Si species. The lack of bands at λ > 300 nm confirms that there is no anatase in most of the synthesized samples.

In IR spectroscopy, the band at about 960 cm^{-1} corresponds to the stretching Si-O vibrational mode perturbed by the presence of framework titanium (Fig. 4).

So with these methods we are sure that we obtain a highly crystalline materials, containing Ti atoms incorporated in zeolites' matrix.

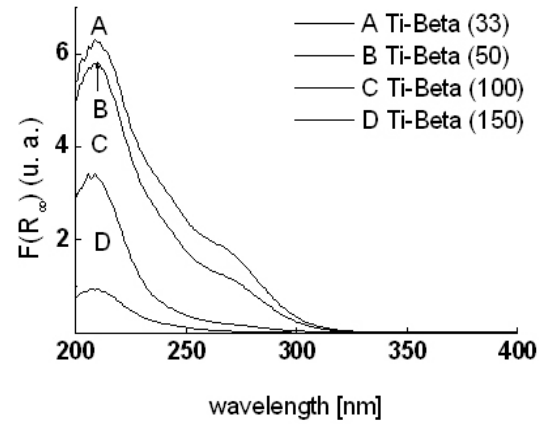

Fig. 3. UV-VIS spectra for some synthesized Ti-Beta samples. Different Ti:Si ratios – 1:33 (A), 1:50(B), 1:100(C) 1:150 (D).

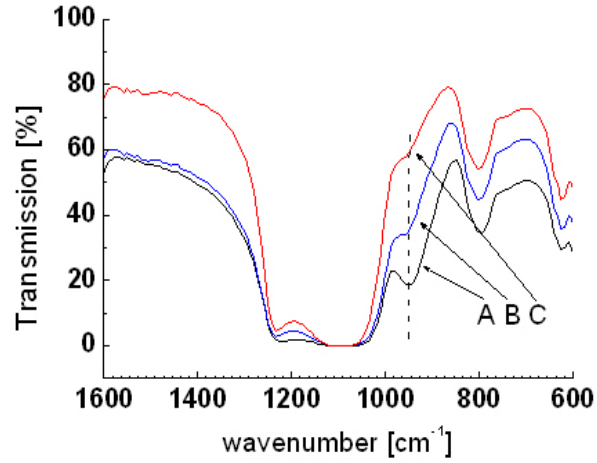

Fig. 4. IR spectra of some synthesized Ti-Beta samples. Different Ti:Si ratios – 1:33 (A), 1:50(B), 1:100(C).

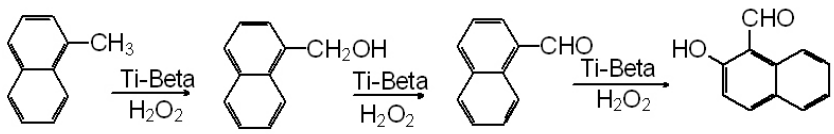

Fig. 5. Oxidation of 1-methylnaphthalene over Ti-Beta to 2-hydroxy-1-naphth-aldehyde.

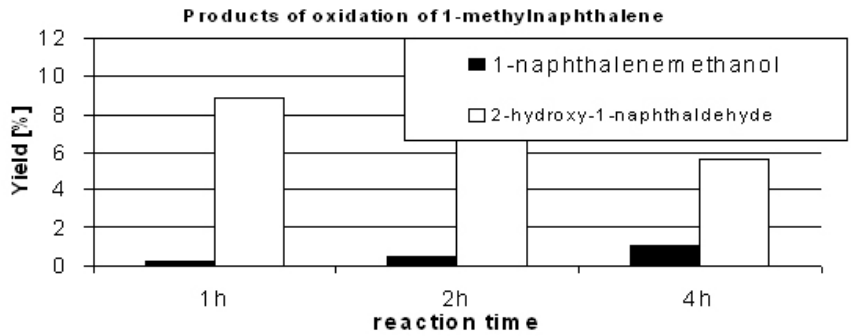

Fig. 6. Products of catalytic oxidation of 1-methylnaphthalene.

Step 1.

After 1 hour reaction time, the main product was 2-hydroxy-1-naphthyl-aldehyde (over 8 %), additionally a small amount (< 1 %) of 1 naphthalenemethanol was detected (using HPLC and references), (Fig. 5). An oxidation only in the ring is not observed. The same products were obtained after 2 h reaction time, but the yields increased to 10 % for 2 hydroxy-1-naphthaldehyde and over 1 % for 1 naphthalenemethanol. After 4 hours (Fig. 6) the reaction proceeded in the same two directions but the concentration of aldehyde in the mixture decreased to 6 % and the concentration of alcohol increased to 1 %. Other products of oxidation (> 5 %) were also noticed in the chromatograms, but they could not be analyzed precisely due to low intensities and overlapping of the peaks. Probably, the prolongation of the reaction time leads to further deeper oxidation of substrate resulting in the formation of polynaphthols, which are generally hard to detect by HPLC.

Steps 2-3.

After 1 h the main yield of 2 hydroxy-1-naphthylhydrazone was 70 % and the main yield of (**1**) (step 3) was 80 %. May be here, the reaction conditions could be further optimized (i.e. variability of solvent). Interesting is that the hydrazone structure can be recognized from the active center of the HIV-1/2 reverse transcriptase DNA polymerase as a nucleotide pair (Fig. 7). The enzyme tries to separate into two "nucleotides", but this is impossible since the bonds are covalent. Thus, the enzyme molecule is blocked in its activity. Our further investigation planned are to prove the inhibitor activity of a compound (1).

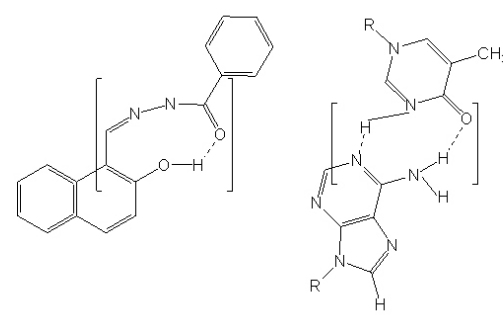

Fig. 7. (**1**) and thymine-adenine pair.

CONCLUSIONS

Ti-Beta oxidizes 1-methylnaphthalene relatively deep to 2 hydroxy-1-naphthaldehyde. Oxidation takes place predominately at ring and side chain position, only small amounts of oxidation products, exclusively in the side chain (< 1 %) relative to 1 naphthalenemethanol, were detected

The selectivity for 2 hydroxy-1-naphthaldehyde decreases for reaction times exceeding 2 hours, since other non-identified polyalcohols or polyaldehydes are formed.

As aldehyde 2 hydroxy-1-naphthaldehyde, it can easy react with hydrazine hydrate to hydrazone and further with another aldehyde to azine in an addition-elimination reaction.

The aminobenzoyl-2 hydroxy-1-naphthyl hydrazone is HIV-1 RT RNase H inhibitor and effective against a variety of drug-resistant HIV-1 RT mutants.

Acknowledgements

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