



# Unexpected dimerization of a nitrobenzyl chloride under basic conditions

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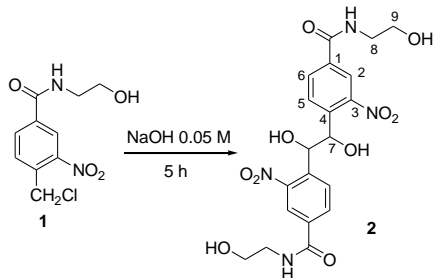
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## INTRODUCTION

The 4-(chloromethyl)-3-nitro-*N*-(2-hydroxyethyl)-benzamide (**1**), previously synthesized by our research group, is a promising antitumor agent whose activity *in vitro* and *in vivo* has recently been investigated<sup>1</sup>. Forced degradation studies are an important part of drug development process, which allows to identify the degradation products and to determine the intrinsic stability of the molecule. In this work, we describe the results of degradation studies of **1** under hydrolysis conditions.

## RESULTS AND DISCUSSION

Compound **1** was treated with aqueous 0.05 M NaOH for 5h at room temperature. An unexpected product was formed (63% yield), which was identified as the dimer **2** (scheme 1). When the hydrolysis was carried out under acid (0.1 M HCl at 80°C) conditions, only the corresponding benzyl alcohol was obtained. These results suggest that the dimerization is favored in basic conditions.



Scheme 1. Synthesis of the dimer **2**.

Compound **2** was characterized by FTIR, NMR, and ESI-MS. The IR spectrum of **2** showed that the characteristic absorption band of hydroxyl groups at 3430 cm<sup>-1</sup> is much more intense compared to the corresponding band in the spectrum of **1**. In the <sup>1</sup>H NMR spectra of **2**, the observation of a signal at 4.64 ppm, integrating to a relative value of 1, indicated the presence of a methine group (H-7). <sup>1</sup>H NMR analysis was supported by the DEPT-135 NMR spectral analysis. The presence of the hydroxyl group attached to C-7 was deduced on the basis of the chemical shift (59.55 ppm) typical of a hydroxylated methine carbon (figure 2). The

simplicity of the NMR spectrum is consistent with a symmetrical molecular structure.

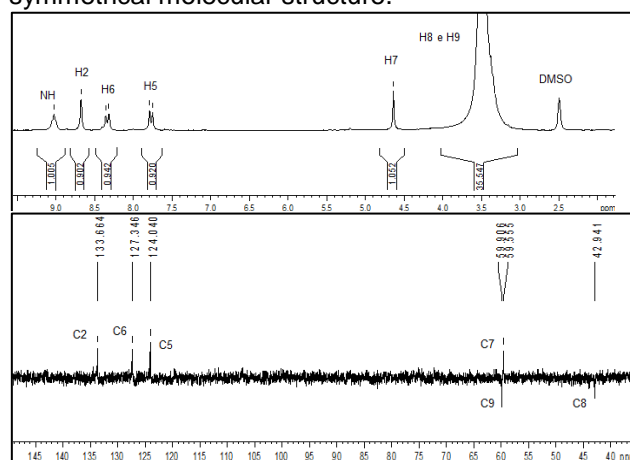


Figure 2. NMR spectra of **2**.

The ESI-MS spectra of **2** in the positive ion mode showed an intense ion of *m/z* 461, corresponding to the dehydrated protonated molecular ion [M+H-H<sub>2</sub>O]<sup>+</sup> (figure 3).

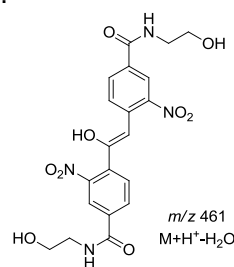


Figure 3. Proposed structure of the fragment ion from ESI-MS.

## CONCLUSION

An unexpected dimeric product was synthesized and characterized by spectroscopic techniques. Further studies on analogues of **1** are in progress in order to investigate the reaction mechanism.

## ACKNOWLEDGEMENTS

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## REFERENCES

<sup>1</sup>Oliveira, R. B. et al. PCT 003563 A1, 2012.