

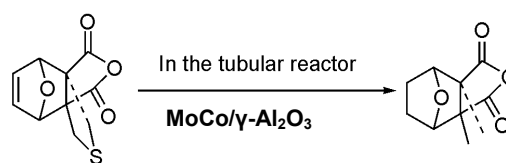
MoCo/ γ -Al₂O₃-CATALYZED HYDRODESULFURIZATION TO SYNTHESIS OF CANTHARIDIN-BASED MOLECULES**

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In the tubular reactor, Hydrodesulfurization on the 7-ox-9-thiortriclo[3^{2,3}.2.2.1]heptanes-5-ene-2,3-dicarboxylic acid (**A**) and Nordehydrocantharidin (**B**) have been accomplished for the first time in the presence of MoCo/ γ -Al₂O₃ with the goal of obtaining pharmacologically promising Cantharidin-based molecules. The yields of Cantharidin (**C**) and Norcantharidin (**D**) were 71% and 80%. And the structure of compounds **C** and **D** was confirmed by ¹H-NMR and ¹³C-NMR, NOESY and ESI-MS. We envisage that this process could be further developed at an industrial scale for the synthesis of Cantharidin-based molecules.



Cantharidin (**C**) is an important natural antineoplastic drug and gave from cantharis in the past long time.^{1,2} It is widely used in various anticancer, such as liver cancer,² cervical cancer,³ skin cancer,⁴ bone marrow cancer and leukaemia,⁵ oesophagus carcinoma and gastric cancer.⁶ **C** has been an enticing. But it cannot be obtained in industrial scale, due to be lack of cantharis. It is very important for total synthesis of **C**. For a long period of time, the synthesis of Cantharidin-based molecules was carried out using Raney Ni or Pd/C as the catalyst in the reaction kettle.⁷⁻¹⁵ However, in the Hydrodesulfurization reaction, Raney Ni or Pd/C as the catalyst were carcinogenic and easily to be spontaneous combustion in air. Especially, the authors got **A** by total synthesis in an ionic-liquid system under ordinary pressure and temperature.² These advantages offer good opportunities for the industrial production of Cantharidin-based molecules. So, it is very important to find the safely and economically catalyst to give Cantharidin-based molecules by Hydrodesulfurization reaction.

The present study, taking **A** and **B** for examples, we were the first to accomplish Hydrodesulfurization in the presence of MoCo/ γ -Al₂O₃ to give **C** and Norcantharidin (**D**) in the tubular reactor. MoCo/ γ -Al₂O₃ is extensively used to Ultra-Deep Hydrodesulfurization of Diesel Catalysts¹⁶; however, the reaction what MoCo/ γ -Al₂O₃ catalyzed **A** or **B** to give **C** and **D** in the tubular reactor has not been reported so far.

In the Fig. 1, the solid of freshly prepared MoCo/ γ -Al₂O₃¹⁷⁻¹⁸ (150 g) were added to the tubular reactor under the nitrogen atmosphere. Then, both the temperature of tubular reactor and preheater equipment were at 280°C. The flow rate of nitrogen and hydrogen were 1 mL/min and 3 mL/min. After a few minutes, the solution of **A** (5 g) in the ethyl acetate (100 mL) were pumped through the vessel at a preset flow rate to 20 mL/min. The mixture was received and cooled to room temperature by the single double-pipe cooler. The mixture was evaporated to afford **C** as a white solid, 3.2 g. Yield: 71%; m.p: 210-212°C; ¹H NMR(600 MHz, CDCl₃) δ ,

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**Supplementary information on <http://web.icf.ro/rrech/> or <http://revroum.lew.ro>

ppm: 1.23(s, 6H), 1.76(m, J=8.4 Hz, 4H), 4.71(d, J=6.0 Hz, 2H); ^{13}C NMR(600 MHz, CDCl_3) δ , ppm: 12.7, 23.4, 55.2, 84.7, 175.9; ESI-MS: m/z 197.08 ($\text{M}+\text{H}^+$, 100%). And, the NOESY of **C** was in the Fig. 2.

Repeat the procedures, **A** was replaced by **B** to give Norcantharidin(**D**) as a white solid. Yield: 80%; m.p: 113-116°C; ^1H NMR (600 MHz, CDCl_3) δ , ppm: 1.62(m, 2H), 1.88(m, 2H), 3.17(s, 2H), 5.02(m, 2H); ^{13}C NMR (600 MHz, CDCl_3) δ ppm: 28.1, 50.6, 80.2, 171.2.

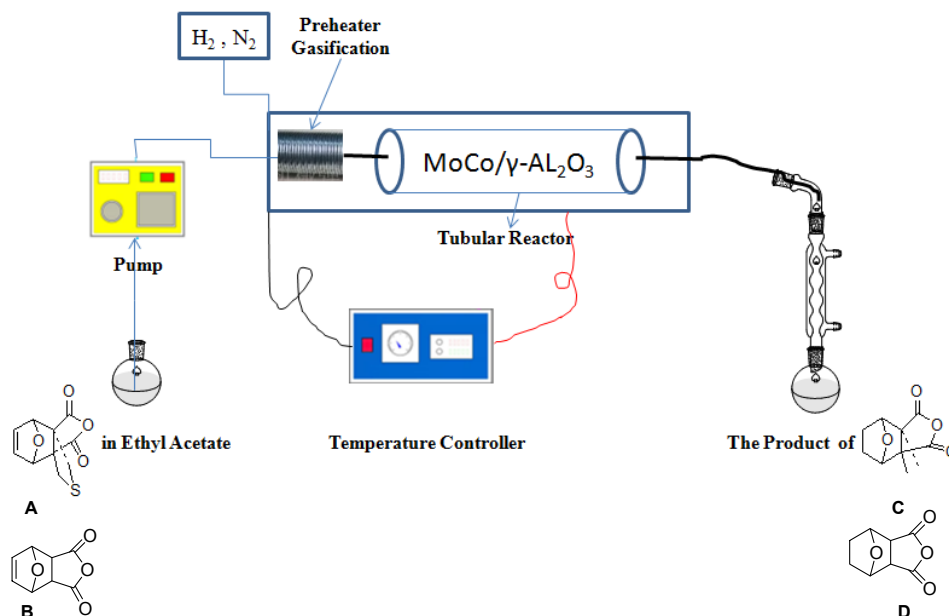


Fig. 1 – $\text{MoCo}/\gamma\text{-Al}_2\text{O}_3$ catalyzed **A** or **B** to give **C** and **D** in the tubular reactor.

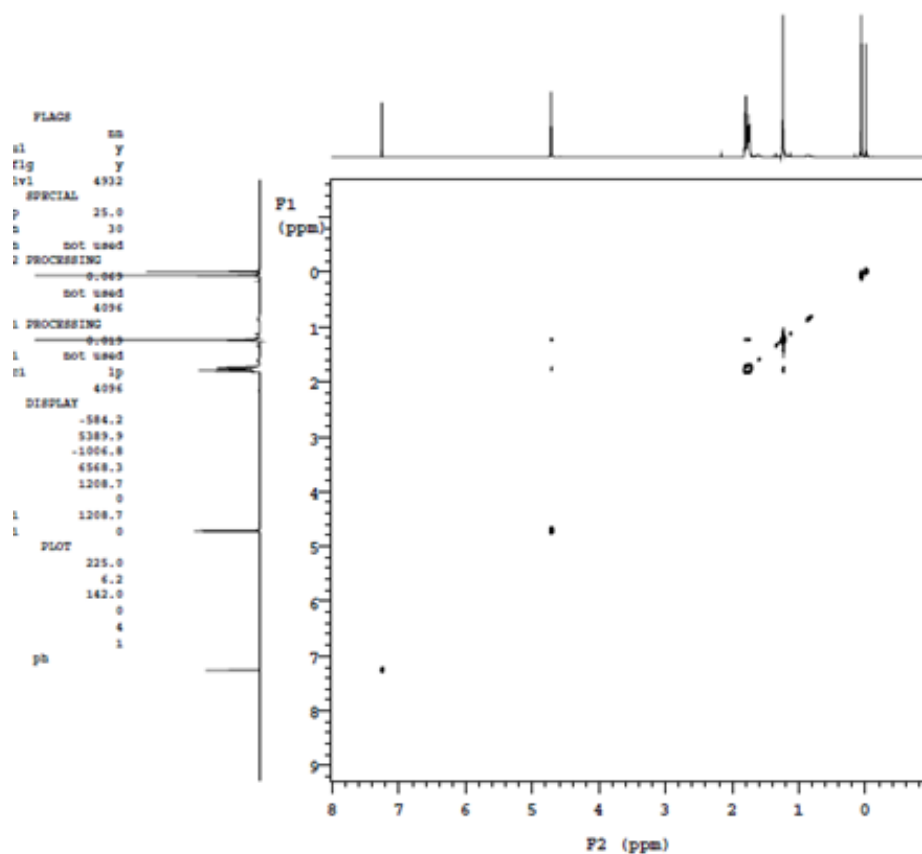


Fig. 2 – The NOESY of **C**.

This study provides a new method for preparation of **C** or **D** and the MoCo/ γ -Al₂O₃ is excellent catalyst. In the tubular reactions, the operation is simple and the product post-treatment is convenient and with high safety, low cost advantages. These advantages also offer good opportunities for the industrial production of Cantharidin-based molecules.

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