



## Synthesis of New Mitotane Analogues

Amanda S. Santana, Felipe R. Sampaio, Carlos Roque D. Correia\*

Chemistry Institute, State University of Campinas – UNICAMP – Campinas-SP

\*roque@iqm.unicamp.br

Keywords: Heck-Matsuda reaction, medicinal chemistry, gram scale

### INTRODUCTION

Mitotane (**1**) is a therapeutic agent used in the treatment of a rare type of carcinoma of the adrenal cortex. This cancer affects children particularly in the states of Paraná and São Paulo.<sup>1</sup> Despite its proven therapeutic efficacy, the mitotane **1**, a chemical congener of the insecticide DDT (**2**), has high toxicity. It is believed that its toxicity is associated with the formation of the corresponding acid chloride in the body.<sup>2</sup> Thus, this work aims at preparing new mitotane analogues that might have reduced toxicity.

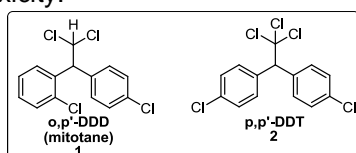
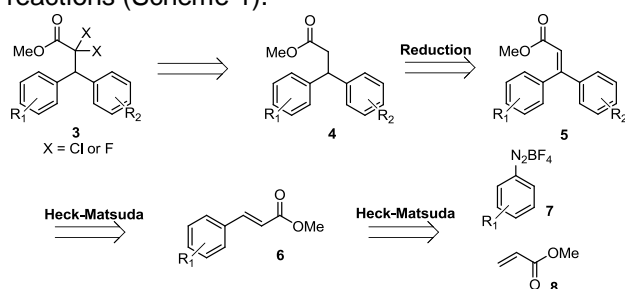


Figure 1. Structure of mitotane and insecticide DDT.

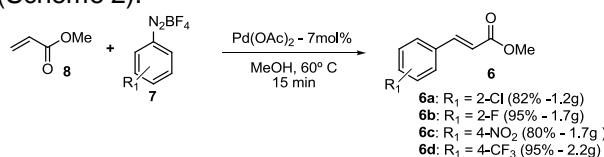
### RESULTS AND DISCUSSION

The strategy proposed to synthesize analogues of mitotane **3** is the  $\alpha$ -carbonyl dihalogenation of **4**. These compounds can be prepared by the reduction of **5** which can be obtained from two consecutive Heck-Matsuda reactions (Scheme 1).



Scheme 1. Retrosynthetic strategy to mitotane analogues.

The methyl cinnamates **6** were prepared in excellent yields at gram scale through a method previously developed in our research group (Scheme 2).<sup>3</sup>



Scheme 2. Methyl cinnamates synthesized.

After several tests, the desired  $\beta,\beta$ -disubstituted acrylates were prepared in an alternative reaction medium employing PEG 400 as solvent (Table 1).

Table 1.  $\beta,\beta$ -disubstituted acrylates obtained.

Entry	R <sub>1</sub>	R <sub>2</sub>	Yield (%) <sup>a</sup>
1	2-Cl	4-Cl	85
2	2-F	4-F	74
3	2-F	4-Cl	75
4	4-NO <sub>2</sub>	4-Cl	50
5	4-CF <sub>3</sub>	4-Cl	60
6	4-CF <sub>3</sub>	2,4-Cl	65

<sup>a</sup> Isolated yield.

Several  $\beta,\beta$ -disubstituted acrylates were obtained in moderate to good yields when the reactions were scaled-up.

### CONCLUSION

It was demonstrated that using mild conditions reactions the Heck adducts could be prepared in gram scale. Biological tests are ongoing.

### ACKNOWLEDGEMENTS

We are grateful to CAPES, CNPq, FAPESP and IQ-UNICAMP to financial support.

### REFERENCES

- 1 AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA, March 15, 1985.
- 2 Figueiredo, B. C.; Sandrini, R.; Ribeiro, R. C.; Lacerda, L.; Pianovski, M. D. *Tumores de Córtex Adrenal*, 2004, 2a ed. Governo do Paraná.
- 3 (a) J. C. Pastre, C. R. D. Correia, *Adv. Synth. Catal.* **2009**, 351, 1217. (b) J. G. Taylor, C. R. D. Correia, *J. Org. Chem.* **2011**, 76, 857. (c) Pastre, J. C.; Correia, C. R. D. *Org. Lett.* **2006**, 8, 165.