

# The use of 2,2,6-trimethyl-4H-1,3-dioxin-4-one (TMD) in multi-component reactions. Synthesis of acetoacetanilides, pyridones and dihydropyrimidines.

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## INTRODUCTION

Multi-component reactions, where more than two reagents combine to give a product in a one-pot process, are efficient methods for the construction of otherwise complex skeletal structures.<sup>1</sup> An important group of substrates for such reactions are 1,3-dicarbonyl compounds.<sup>2</sup> One of the oldest multi-component reactions known is the Biginelli reaction.<sup>3</sup> This three component reaction involves the condensation of urea, ethyl acetoacetate and a benzaldehyde. Biginelli products, dihydropyrimidines, possess a wide variety of biological activities.<sup>4</sup>

In this study we investigated the reaction of TMD (1) with anilines (2) for the preparation of acetoacetanilides (3) in apolar (toluene and xylene) and polar protic (water) solvents. Additionally, the one pot four component reaction involving 1, 2, urea (4) and benzaldehydes (5) to give Biginelli products (6) was studied (Figure 1).

## RESULTS AND DISCUSSION

The reaction of 1 with 2 in xylene or toluene, at reflux, was found to result in the formation of 3 (30% [R<sub>1</sub> = 4-Cl] to 83% [4-Br]) as described in the literature<sup>5</sup> but also in the formation of pyrid-4-one derivatives (7) that required chromatographic separation. The formation of the latter condensation products has not been previously described for this reaction. The pyridones 7 were obtained in 7-41% yields. Due to the poor chemoselectivity of the reaction in apolar solvents we decided to investigate the use of water. Heating 1 and 2 in boiling water resulted in the exclusive formation of 3. These could be isolated by simply allowing the reaction to cool resulting in the crystallization of 3. Alternatively, the aqueous phase was removed under reduced pressure and the crude product filtered through a short column of silica eluting with CH<sub>2</sub>Cl<sub>2</sub> to give 3 (48% [4-F] - 77% [4-Cl] yields).

The successful chemoselective preparation of 3 in an aqueous medium prompted the investigation of a modified Biginelli reaction involving the one pot four component coupling of 1, 2, 4, and 5. Initially, the combination of the four reagents in water under

reflux did not result in the formation of 6. However, when the reaction was conducted in two steps, firstly the preparation of 3 in water (followed by the removal of the water), and secondly, the addition of an ethanol solution of 4 and 5, the Biginelli products 6 were obtained in excellent yields (64-86%). All products were physically and spectroscopically characterized.

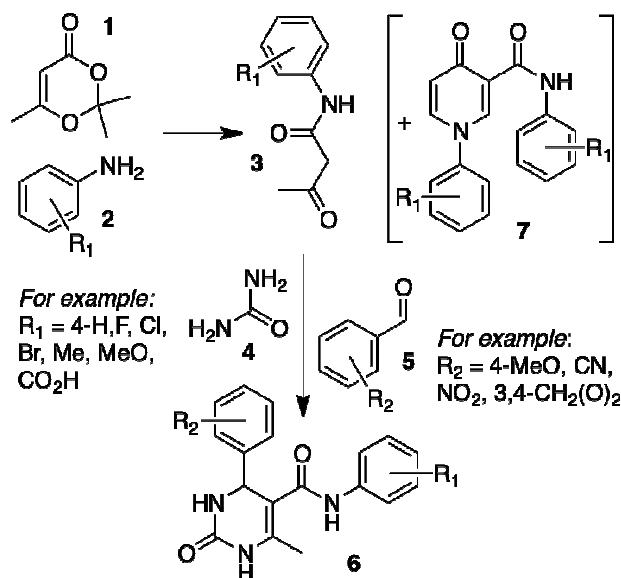


Figure 1. Obtention of 3, 6 and 7.

## CONCLUSION

Acetoacetanilidas are chemoselectively prepared from TMD and anilines in aqueous medium thus avoiding the formation of the pyridones. A one pot four component Biginelli reaction was developed.

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## REFERENCES

- Kumaravel, K. Vasuki, G. *Curr. Org. Chem.*, **2009**, *13*, 1820.
- Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957.
- Souza, R.O.M.A.; Penha, E.T.; Milagre, H.M.S.; Garden, S.J.; Esteves, P.M.; Eberlin, M.N.; Antunes, O.A.C. *Chem. Eur. J.* **2009**, *15*, 9799.
- Wan, J. P., Liu, Y. *Synthesis*, **2010**, 3943.
- Huggins, M. T., Barber, P. S., Florian, D., Howton, W., *Synth. Commun.*, **2008**, *38*, 4226; Clemens, R. J., Hyatt, J. A., *J. Org. Chem.*, **1985**, *50*, 2431.