On the Biginelli Reaction under Homogeneous Catalysis

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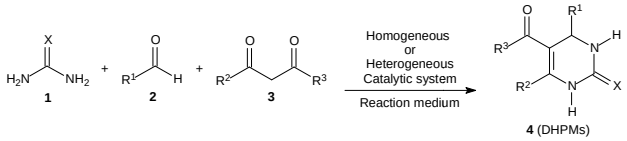
INTRODUCTION

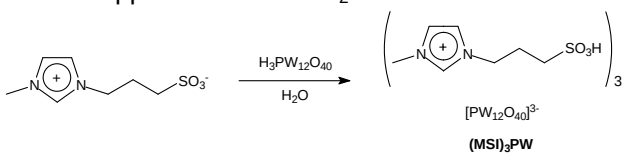
Today, new and greener technologies are imperative needs regarding the chemical industries. Attempts to connect the advantages of catalysis in ionic liquids (ILs)[1] with multicomponent (MCRs) reactions are found.[2] The Biginelli MCR (Scheme 1) was therefore performed with an efficient new homogenous catalytic system towards DHPM synthesis in ILs with an imidazolium Bronsted IL bearing $[PW_{12}O_{40}]^{3-}$.



Scheme 1. General catalyzed Biginelli reaction.

RESULTS AND DISCUSSION

Scheme 2 shows the catalyst synthesis, which was further supported in BMI.NTf_2 for the reaction.



Scheme 2. Synthesis of the homogeneous catalyst **$(MSI)_3PW$**.

Fifteen different DHPMs, including the bioactive Monastrol, were synthesized in good to excellent yields (60-99%). To investigate the mechanism, ESI-QTOF-MS analyses were performed (Figure 1).

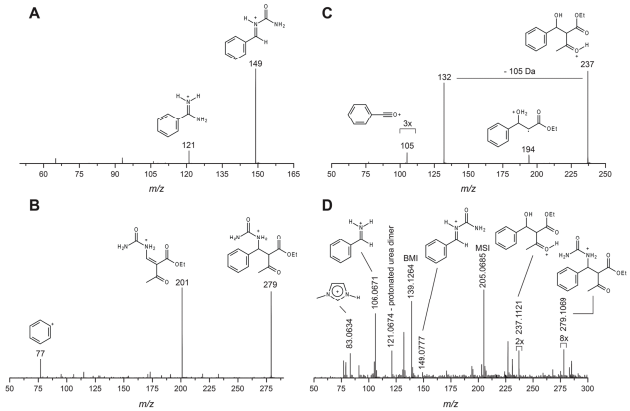


Figure 1. (A)–(C) ESI(+)-QTOF of the key intermediates.(D) ESI(+)-QTOF mass spectrum of the reaction.

The iminium mechanism was clearly the preferred reaction pathway as indicated by the detection of the iminium intermediate (**Int I**, Figure 1A) and the intermediate from the addition reaction to this ion (**Int II**, Figure 1B).

Finally, to gain insights into the mechanism and mainly into the IL effect, DFT calculations were also performed (Figure 2) considering the anion (NTf_2) effect over the charged cationic intermediates detected by ESI-MS analyses.

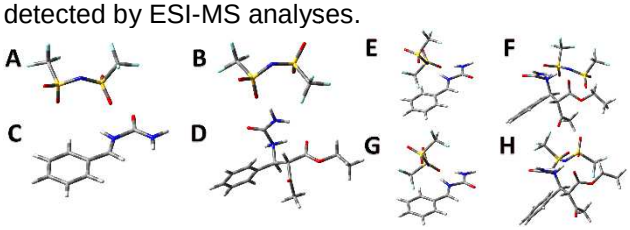


Figure 2. Optimized geometries at B3LYP/6-31+G(d,p) level of theory. (A) Anion (NTf_2) *cis*. (B) Anion (NTf_2) *trans*. (C) **Int I** (iminium). (D) **Int II** (addition to the iminium). (E) **Int I** associated with the anion NTf_2. Note the anion changed to its *trans* conformation upon approximation. (F) **Int II** associated with the anion NTf_2 (*cis*). (G) **Int I** associated with the anion NTf_2 (*trans*). (H) **Int II** associated with the anion NTf_2 (*trans*).

The anion (NTf_2) from the IL (reaction medium) stabilized the charged (cationic) key intermediates upon ion pairing (and larger supramolecular aggregates) formation.

CONCLUSION

The efficiency of the new homogeneous catalytic system (**$(MSI)_3PW$**/BMI.NTf_2) to perform the Biginelli MCR with enhanced IL effect was demonstrated.[3] ESI-MS analyses and DFT calculations pointed the preferred mechanism pathway (iminium) and the origin of the IL effect through both ion pairing and larger supramolecular aggregates formation.

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CAPES, CNPq, FAPDF, FAPESP and DPP-UnB.

REFERENCES

1 Dupont, J.; Souza, R. F.; Suarez, P. A. Z. *Chem. Rev*. **2002**, *102*, 3667.
2 de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev*. **2012**, *41*, 3969.
3 Alvim, H. G. O.; de Lima, T. B.; de Oliveira, H. C. B.; Gozzo, F. C.; de Macedo, J. L.; Abdelnur, P. V.; Silva, W. A.; Neto, B. A. D. *ACS Catal.* **2013**, *3*, 1420.