



Organocatalysis in the Three-Component Povarov Reaction and Mechanistic Investigation by Mass Spectrometry

Juliana B. Simões^{1,2}, Ângelo de Fátima³, Adão A. Sabino³, Francisco J. T. Aquino³, Daniel L. Silva³, Luiz Claudio A. Barbosa^{1,3}, Sergio A. Fernandes^{1*}

¹ Department of Chemistry, CCE, Universidade Federal de Viçosa, Viçosa, MG, 36570-000, Brazil.

² Department of Science Education, Instituto Federal Fluminense, Itaperuna, RJ, 28300-000, Brazil.

³ Department of Chemistry, ICEx, Universidade Federal de Minas Gerais, Belo Horizonte, MG, 31270-901, Brazil.

*santonio@ufv.br or sefernandes@gmail.com

Keywords: *p*-sulfonic acid calix[4]arene, julolidines, diastereoselective reaction.

INTRODUCTION

The advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy.¹ In this work *p*-sulfonic acid calix[4]arene (CX4SO₃H) was employed as a organocatalyst to promote a three-component Povarov reaction, for the preparation of julolidines.² Julolidines and derivatives are endowed with interesting scientific and industrial applications.³

RESULTS AND DISCUSSION

For a model reaction 4-bromoaniline (**1b**), formaldehyde (**2**) and styrene (**3**) were employed the Table 1 presented the results of optimization.

Table 1. Optimization of reaction conditions^a

Entry	Catalyst (mol%)	Solvent	Time (h)	4b Yield (%) ^b	4b de (%) ^e
1	CX4SO ₃ H (25)	CH ₃ CN	1	54	50
2	CX4SO ₃ H (25)	CH ₃ OH	1	61	72
3	CX4SO ₃ H (25)	DMF	1	30	60
4	CX4SO ₃ H (25)	Diethyl Carbonate	1	24	58
5	CX4SO ₃ H (25)	Ethyl lactate	1	8	61
6	CX4SO ₃ H (25)	H ₂ O	1	64	74
8	CX4SO ₃ H (2.0)	H ₂ O	1	65	74
9	CX4SO ₃ H (2.0)	H ₂ O	2	70	74
10	CX6SO ₃ H (1.5)	H ₂ O	2	50	72
11 ^c	CX4SO ₃ H (2.0)	H ₂ O	2	15	74
12 ^d	CX4SO ₃ H (2.0)	H ₂ O	2	24	72

^aThe reaction of **1b** (1 mmol), **2** (3 mmol) **3** (3 mmol) was carried at room temperature. ^bIsolated Yield. ^cThe reaction of **1b** (1 mmol), **2** (1 mmol) **3** (1 mmol); yield of **5b** 26%. ^dThe reaction of **1b** (1 mmol), **3** (2 mmol) **3** (2 mmol); yield of **5b** 35%. ^eDetermined by GC/MS.

To prove the efficiency of CX4SO₃H other acids were tested (CF₃COOH, CH₃COOH, PTSA, PHS) and among then only H₂SO₄ afforded the required product **4b** in a reasonable yield of 60%. However, in this case the diastereoisomeric excess (*de*) was negligible (12%). The scope of this protocol is presented in Table 2.

The reaction was monitored by electrospray mass spectrometry and the mechanistic pathway uncovered. The ESI(+)-MS spectrum (Fig. 1) showed five major ions, prompting us to corroborate the stepwise mechanism *via* Mannich-like reaction

followed by an intramolecular electrophilic aromatic substitution.

Table 2. Reaction scope for different anilines^a

Reaction scheme showing the synthesis of julolidine derivatives **4a-m** from anilines **1a-m**, formaldehyde (**2**), and styrene (**3**) using CX₄SO₃H (2 mol%) in H₂O at room temperature (r.t.).

R	Time (h)	Yield (%) ^b	de (%) ^c	R	Time (h)	Yield (%) ^b	de (%) ^c
H	2	75	63	HO	2	68	71
F	2	74	64	SH	2	64	60
Cl	2	76	61	CF ₃	8	70	53
(CH ₃) ₃ C	2	80	31	NO ₂	8	73	45
CH ₃ O	2	83	63	CN	8	72	50
CH ₃ S	2	89	70	CO ₂ H	8	69	46

^a The reaction of an aniline **1a-m** (1 mmol), a formaldehyde **2** (3 mmol) and styrene **3** (3 mmol). ^b Isolated Yield. ^c Determined by GC/MS.

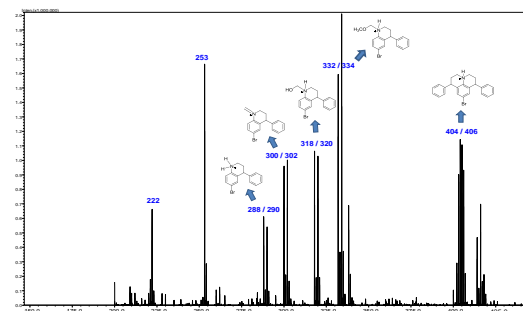


Figure 1. ESI(+)-MS spectrum (30 min.), for the formation of **4b**.

CONCLUSION

We have developed an efficient and diastereoselective three-component reaction for the production of julolidines using CX4SO₃H as a catalyst. Some intermediates for this reaction were probed by the ESI(+)-MS technique, supporting the stepwise mechanistic proposal.

ACKNOWLEDGEMENTS

CNPq, FAPEMIG, FUNARBE and CAPES.

REFERENCES

- a) Mac-Millan, D.W.C. *Nature*, **2008**, *18*, 304. b) Simões, J.B.; Silva, D.L.; Fátima, A.; and Fernandes, S.A. *Curr. Org. Chem.*, **2012**, *16*, 949.
- Simões, J.B.; Fátima, A.; Sabino, A.A.; Aquino, F.J.T.; Silva, D.L.; Barbosa, L.C.A. and Fernandes, S.A. *Org. Biomol. Chem.*, **2013**, *11*, 5069.
- Palma, A.; Agredo, J.S.; Carrillo, C.; Kouznetsov, V.; Stankenko, E.; Bahsas, A. and Amaro L.J. *Tetrahedron*, **2002**, *58*, 8719.