An Efficient Three-step Synthesis of β-Phenethylcinnamamides Toward New Biological Active Compounds

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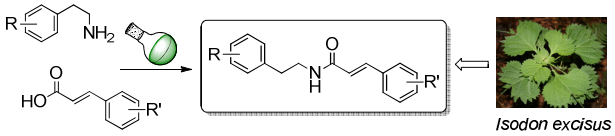
INTRODUCTION

Most of the family members of β-phenethylamides constitute an important part of the natural and synthetic products discover so far.[1] The biological importance of these small molecules (SM) is based on their selectivity to induced apoptosis in different malignant cell lines, including melanoma and leukemia.[2] Due to the value of these amides in cancer research and the difficult to extract their analogues from natural sources, i.e. *Isodon excisus*.[3] The responsibility to develop a novel synthetic protocols that allow the preparation of new libraries of β-phenethylcinnamamides lies on organic chemistry (Scheme 1).



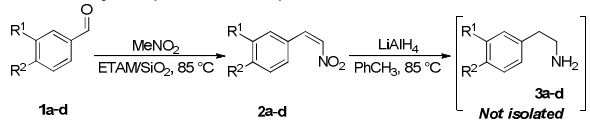
Isodon excisus

Scheme 1. Synthetic and natural sources of phenethylcinnamamides

According to the aspects described above and our current interests in N-phenethylcinnamamides, we designed a strategy for the preparation of these compounds under the parameters of green chemistry and improving some synthetic aspects.

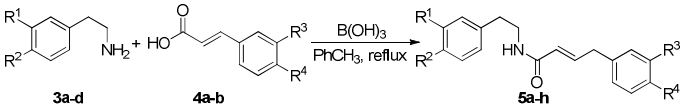
RESULTS AND DISCUSSION

Our synthetic plan required a series of β–phenylethylamines **3a**-**d** that were prepared through the reduction of the corresponding β-nitrostyrenes **2a**-**d**.[4] These nitroalkanes were prepared in excellent yield from the respective aldehydes **1a**-**d** using ethanolamine supported on SiO_2 (ETAM/SiO_2) as a catalyst[5] (Scheme 2).



Scheme 2. Preparation of β-phenylethylamines **3a**-**d**.

In the final stage, each β-phenylethylamine was mixed with boric acid (10 % mol) and *trans*-cinnamic acid **4a-b** in toluene at 110 ºC leading the desired amides **5a**-**h** in good to excellent yields[6] (Scheme 3).



Scheme 3. Synthesis of new β-phenethylcinnamamides.

All products **5a-h** (Table 1) were obtained as stable solids that were characterized by IR, mass spectrometry and NMR (^{1}H, ^{13}C).

Table 1. New β-phenethylcinnamamides obtained.

Comp.	R^1	R^2	R^3	R^4	Yield, %*
5a	H	H	H	H	98
5b	H	H	-OCH$_2$O-		93
5c	H	F	H	H	99
5d	H	F	-OCH$_2$O-		87
5e	H	OMe	H	H	98
5f	H	OMe	-OCH$_2$O-		84
5g	OMe	OMe	H	H	97
5h	OMe	OMe	-OCH$_2$O-		81

*Isolated yield.

Reducing the β-nitrostyrenes in toluene lead the complete conversion (TLC) into the desired amine and allow it's used in the final step without further purification, facilitating their handling and integrity.

CONCLUSION

We have developed an efficient and easy protocol for the synthesis of β-phenethylcinnamamides, from available commercial reagentes, under green and mild conditions. The obtained compounds could serve for a SM screening in different biological systems.

ACKNOWLEDGEMENTS

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