A^3 Coupling Reaction as a Key Strategy in a Three-Step Synthesis of Bioactive Alkaloids

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INTRODUCTION

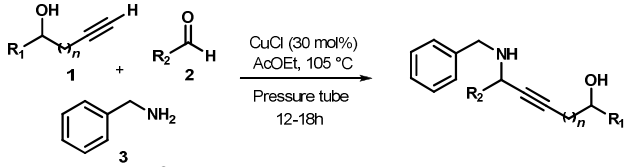
In the last decades the multicomponent reactions have been shown to be an important way to prepare high functionalized compounds within high atom-, energy- and step- economy. One of these compounds are the propargylamines, which are important chiral tools in organic synthesis especially in the pharmaceutical industry. This class of compounds are important building blocks for the preparation of complex amino derivatives and bioactive substances.[1]

An important known strategy for the synthesis of this class of compounds consists in the 1,2-addition reaction of non-functionalized acetylenic organometallics to a C-N double bond, usually of imines, enamines, nitrones and iminium salts.[2]

In this study, we payed attention to develop a three-component one-step coupling, using alkynols, benzylamine and aldehydes to prepare benzylamine propargyl alcohols.

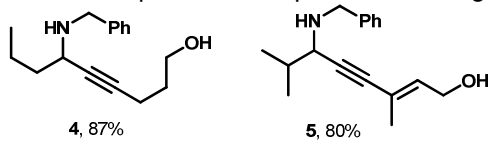
RESULTS AND DISCUSSION

The A^3 coupling using alkynols (**1**), aldehydes (**2**) and benzilamine (**3**) in the presence of catalytic amount of copper (I) chloride (30 mol%) and ethyl acetate, in a pressure tube was found to be a highly efficient reaction condition, as shown in scheme 1.

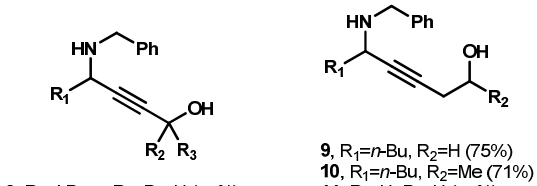


Scheme 1 – A^3 coupling conditions.

A large number of aldehydes and alkynols were submitted to reaction with **3** and the structures and yields of the products are presented in Figure 1.



4, 87% **5**, 80%

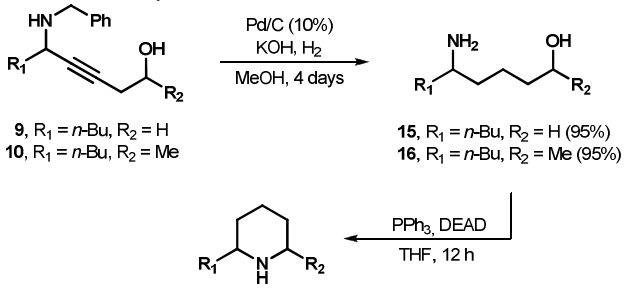


6, R_1=*i*-Prop, R_2=R_3=H (63%)
7, R_1=*n*-Bu, R_2=Me, R_3=H (29%)
8, R_1=*n*-Bu, R_2/R_3=*c*-Hex (56%)

9, R_1=*n*-Bu, R_2=H (75%)
10, R_1=*n*-Bu, R_2=Me (71%)
11, R_1=H, R_2=H (61%)
12, R_1=*c*-Hex, R_2=H (60%)
13, R_1=Ph, R_2=H (64%)
14, R_1=4-Tol, R_2=H (54%)

Figure 1 – Benzylamine propargyl alcohols obtained via A^3 coupling.

Some of these compounds were employed, as starting materials in the synthesis of bioactive alkaloids, as presented in scheme 2.



9, R_1 = *n*-Bu, R_2 = H
10, R_1 = *n*-Bu, R_2 = Me

15, R_1 = *n*-Bu, R_2 = H (95%)
16, R_1 = *n*-Bu, R_2 = Me (95%)

17, R_1 = *n*-Bu, R_2 = H (65%) (±-coniine)
18, R_1 = *n*-Bu, R_2 = Me (63%) (±-dihydropinidine)

Scheme 2 – Benzylamine propargyl alcohols in the synthesis of alkaloids.

CONCLUSION

In summary, we have shown that amino alkynols can be easily prepared in a one-pot three-component reaction in moderate to good yields by A^3 coupling. This methodology demonstrated to be a short and efficient way for the synthesis of bioactive alkaloids.

ACKNOWLEDGEMENTS

CAPES CNPq FAPESP

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