

Synthesis of Building Blocks for the Construction of Trialomethylated Heterocycles

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Keywords: Trialomethylated Heterocycles, Reactions of Horner-Wadsworth-Emmons, Olefination

INTRODUCTION

Many trifluoromethylated heterocycles showing remarkable biological activity have been widely used in a variety of fields ranging from medicine to agricultural products, besides of being versatile intermediate for the synthesis of biologically active compounds containing trifluoromethyl groups. Among these trifluorinated compounds, stand pyridines, which have some approaches to preparation. The general procedures for synthesis of trifluoromethyl-pyridines are generally antimony catalysts, or MoF₆ at high temperature and pressure. An alternative method involves direct introduction of trifluoromethyl groups in pyridine, using CF₃I or CF₃Cl. However, these methods have some disadvantages such as high temperature and pressure, use of HF, low reactivity, low selectivity, limited scope and formation of sub products. Thus, the development of synthetic methods for preparation of trifluoromethylpyridines and other heterocycles, it is highly desired. In this context, the use of simple trifluoromethyl building blocks has often proved to be a better choice than the direct trialomethylation methods.

Therefore, this work aims to developing an efficient methodology for the synthesis of convenient trialomethylated building blocks that will be used for the preparation of trialomethylated heterocycles.

RESULTS AND DISCUSSION

Scheme 1 reports the reaction method used for the synthesis of compounds **6-11a-b**. The synthesis of compounds described in Scheme 1 was based on reactions of Horner-Wadsworth-Emmons of β -alkoxivinyl-trialomethyl-ketones **1-5a-b** and phosphinate **6** in THF with the addition of NaH, leading to the formation of compounds **7-11a-b** in good yields (Table 1). The reactions were carried out under reflux, stirring, and inert atmosphere. After 2h, the reaction mixture was purified by silica column chromatography using methanol/chloroform as eluents.

Figure 1. Synthesis of compounds **7-11a-b**.

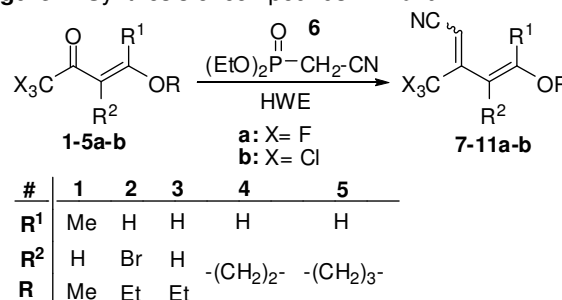


Table 1. Reaction condition used for the synthesis of compounds **7-11a-b** and yields.

#	Enone	Reaction condition ^a	Yield (%) ^b
7a	1	<i>i</i>	36
7b	1	<i>i</i>	30
8a	2	<i>i</i>	76
8b	2	<i>i</i>	60
9a	3	<i>i</i>	71
9b	3	<i>i</i>	81
10a	4	<i>i</i>	49
10b	4	<i>i</i>	60
11a	5	<i>i</i>	80
11b	5	<i>i</i>	55

^a Reactions condition: NC-CH₂P(O)(OC₂H₅)₂, NaH, THF, 66°C, 2h. ^b Yield of isolated products.

CONCLUSION

In this work, we reported a series of novel and important trifluoromethyl building blocks **7-11a-b** that will be used for the preparation of many trialomethylated heterocycles with promising biological potential.

ACKNOWLEDGEMENTS

The authors acknowledge the financial support of CNPq, CAPES and FAPERGS.

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