Regioselective synthesis of 1,3- and 1,5-substituted pyrazoles and pyrazolynes analogous of Celecoxib

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Keywords: pyrazoles, trifluoromethyl, sulfamide

INTRODUCTION

The analgesic action of pyrazoles is widely studied and among the commercially available drugs containing the pyrazoline nucleus can be highlighted dipyrone and Celecoxib.[1]

Celecoxib (Celebrex™) is a non-steroidal anti-inflammatory used in the treatment of diseases such as rheumatoid arthritis. It was the first selective inhibitor of cyclooxygenase 2 (COX-2) launched in the world, however, there are several questions about their toxicity, especially with regard to the cardiovascular system.[2]

Some methodologies for the synthesis of Celecoxib have been described, but often resulting an isomeric mixture of pyrazoles (1,3- and 1,5-substituited) difficult to separate.

4-alkoxyvinyl trifluoromethyl ketones are important precursors blocks. From these ketones is possible to synthesize a series of heterocycles, including pyrazoles[3] and, therefore, this work aims to regioselective synthesize a series of 1,3- and 1,5-substituted sulfamidophenyl pyrazoles.

RESULTS AND DISCUSSION

Pyrazoles **3**, **4** and **5** were synthesized by three different methodologies, from cyclocondensation reaction of 4-alkoxyvinyl trifluoromethyl ketones (**1a-f**) and 4-sulfamidophenylhydrazine hydrochloride (**2**). In all the methods tested, we used a stoichiometric ratio between 1,3-dieletrofile and hydrazine. In the first method, MeOH was used as solvent and 0.5 mL of a 1 M solution of Na_2CO_3 was added at room temperature for 3 h. This methodology gave the pyrazolines **3a-f**, in the form of 1,5-substituted regioisomers, which were subsequently dehydrated by a solution of MeOH/HCl 1:10, under reflux, for 1 h, to render only the 1,5-somer of pirazoles **4a-f**. The pirazoles **4a-f** were isolated in a pure form by neutralization of the reaction mixture with 1M NaOH solution followed by extraction from ethyl acetate.

For the series of pyrazoles **5**, initially occurred hydrolysis reaction of compounds **1** by addition of 1 mL of hydrochloric acid to a methanolic solution of **1a-f** for one hour at room temperature. Then, hydrazine **2** was added and the temperature was raised to reflux for 3 h. The pyrazoles **5a-f** were isolated by neutralization of the reaction mixture with 1M NaOH solution followed by extraction from ethyl acetate. Pyrazoles **5a**, **5d** and **5f** were obtained only as the 1,3-isomers and pirazoles **5b-c** and **5e** were obtained in a ratio of 9:1 in favor of the 1,3-isomer.

The products were identified by ^1H and ^{13}C NMR and GC-MS (EI).

Scheme 1. Synthesis of compounds **3a-f, 4a-f** and **5a-f**

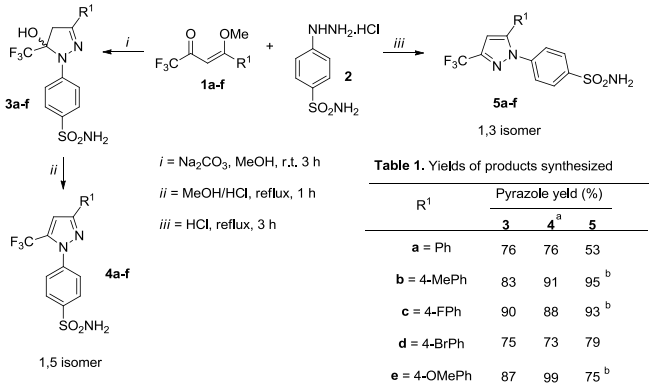

Table 1. Yields of products synthesized

R^1	Pyrazole yeld (%)		
	3	**4**[a]	**5**
a = Ph	76	76	53
b = 4-MePh	83	91	95[b]
c = 4-FPh	90	88	93[b]
d = 4-BrPh	75	73	79
e = 4-OMePh	87	99	75[b]
f = 2-Furyl	97	93	77

[a] only 1,5-regioisomer
[b] mixture of 1,3 and 1,5 regioisomers in ratio 9:1

CONCLUSION

In conclusion, we found a simple and regioselective method to obtain both 1,3- and 1,5-isomers of pyrazoles analogous of Celecoxib.

ACKNOWLEDGEMENTS

The authors thank the financial support from CNPq, CAPES and FAPERGS.

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