New one-pot and regioselective method for the synthesis of 3-trifluoromethyl-1*H*-1-phenylpyrazoles

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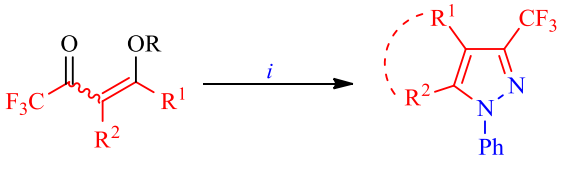
Keywords: 3-Trifluoromethylpyrazoles, Cyclization reactions, Phenylsemicarbazides

INTRODUCTION

Pyrazoles derivatives has been extensively explored by our research group contemplating their biological activities.[1] Efficient approaches to introduce a CF_3 group at the C-3 position of pyrazole ring in a regioselective manner has been getting attention, mostly because these compounds often show pharmacological activities such as the anti-inflammatory Celecoxib® and the anticoagulant Razaxaban® and the anticoagulant Razaxaban®. So, we report an efficient and regioselective insertion of a CF_3 group into pyrazole rings from the reaction of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones [$CF_3C(O)CH=CR^1(OR)$ where R = Me or Et, R^1 = H, Me, Ph, 2-Furyl and R^1-R^2 = -C_4H_8-] (**1a-e**) and 1-phenyl-semicarbazide (**2**) in order to obtain 3-trifluoro-methyl-1-phenylpyrazoles (**3a-e**) as the main isomer.

RESULTS AND DISCUSSION

The optimized synthesis of 3-trifluoromethyl pyrazoles (**3a-e**) was carried-out in the presence of sulfuric acid and methanol as the reaction solvent and in a 1:1.5 molar ratio (**1a-e**:**2**), stirring the mixtures at 60 °C for 24 h (Scheme 1).[2] All **3a-e** structures were confirmed by ^1H and ^{13}C NMR and mass spectrometry (GC-MS) data analysis and by comparison to the 5-trifluormethyl-1*H*-pyrazole isomers previously acquired.[3]



1a-e **3a-e**

1,3	a	b	c	d	e
R^1	H	Me	-	Ph	2-Furyl
R^2	H	H	-	H	H
R^1-R^2	-	-	-C_4H_8-	-	-

Scheme 1. Reagents and conditions: (*i*) $Ph(NH)_2CONH_2$ (**2**), MeOH, H_2SO_4 conc., 60 °C, 24 h (50 – 85 %).

Thus, we identified and easily proved that the 3-CF_3-substituted pyrazole regioisomers were isolated through this new present methodology (Table 1).

Table 1. Yields and isomer relations for compounds **3a-e**.

Product	Yield(%)[a] / (Lit.)[b]	Isomer 1,3:1,5[c] / (Lit.)[b]
3a	50 / (16), (94)	50:50 / (100:0)
3b	77 / (70), (80)	100:0 / (50:50)
3c	54	97:3
3d	65 / (-[d]), (65)	100:0 / (82:18), (100:0)
3e	85 / (-[d])	100:0 / (100:0)

[a]Yields of isolated products. [b]Literature data. [c]GC-MS data analysis. [d]Uninformed yields from literature data.

CONCLUSION

We have developed a mild, convenient and improved protocol for the regioselective synthesis of 3-trifluoromethyl-1*H*-1-phenylpyrazoles in methanol and sulfuric acid as catalyst. This new method is simple and efficient for achievement of region-selective products. Compounds **3a-e** were obtained as dark-yellow oils in 50 – 85 % yields. Complete results are covered in our patent and in a recent published paper.[2]

ACKNOWLEDGEMENTS

CNPq - CAPES

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