Synthesis of new biheterocyclic 4-(2-(1,3,4-oxadiazol-2-yl)ethyl)-6-(trifluoromethyl)pyrimidines

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INTRODUCTION

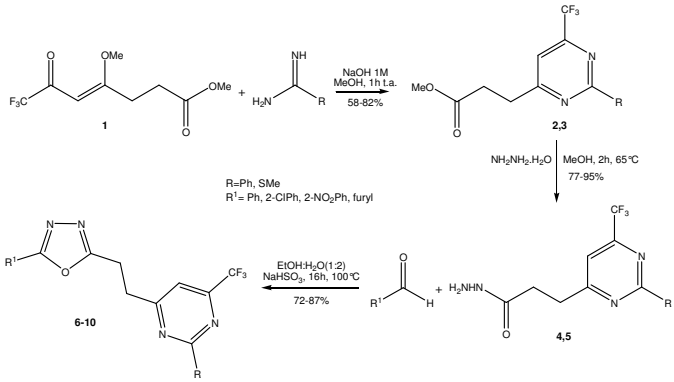
Among the heterocyclic compounds pyrimidines and oxadiazoles stand out because of their biological and medicinal importance. Pyrimidines have been used as antibiotics, antineoplastic, among others.[1] On the other hand, 1,3,4-oxadiazoles have been identified as the main core of many bioactive molecules exercising antiinflamatory, antimicrobial and anticonvulsant activities.[2]

In recent years we have focused our interest on methyl 7,7,7-trihalo-4-methoxy-6-oxo-3-heptenoates. These represent significant and versatile halogen-containing building block for the synthesis of heterocyclic systems, which often show high biological activities.[3]

In connection with our studies on the synthesis of azole and pyrazine derivatives we were interested in developing general and convenient methods for the synthesis of biheterocyclic systems from methyl 7,7,7-trihalo-4-methoxy-6-oxo-3-heptenoates. Here we report the synthesis of 4-(2-(1,3,4-oxadiazol-2-yl)ethyl)-6-trifluoromethylpyrimidines (**6-10**) from 3-(6-trifluoromethylpyrimidin-4-yl)propanehydrazide and aromatic aldehydes.

RESULTS AND DISCUSSION

Methyl 7,7,7-trifluoro-4-methoxy-6-oxo-3-heptenoate **1** was synthesized by an acylation method early described the in literature.[3] The cyclocondensation of **1** with benzamidine and S-methylthiourea was investigated. The reaction proceeded in methanol with NaOH for 1 hour at room temperature to give the respective pyrimidines **2** and **3** in good yields.[4] Treatment of methyl 3-(6-trifluoromethylpyrimidin-4-yl)propanoates **2** and **3** with hydrazine hydrate in refluxing methanol afforded the corresponding hydrazides **4** and **5**. Hydrazides **4** and **5** were reacted with aromatic aldehydes in ethanol:water solution under catalysis by $NaHSO_3$ to afford the target biheterocyclic title systems **6-10** (Scheme 1). Compounds **2**-**10** are new, and were synthesized via simple and unexpensive methods. All synthesized compounds were obtained in good yields and high purity as solids and their structures were attributed by $^1H/^{13}C$ NMR and GC/MS data.



Scheme 1. Synthesis of 4-(2-(1,3,4-oxadiazol-2-yl)ethyl)-6-(trifluoromethyl)pyrimidines

CONCLUSION

In summary, this work shows a highly efficient and versatile synthetic route for the obtention of biheterocyclic systems with high potential activity. We use easily manipulable inexpensive reagents in relatively short reaction times producing new trifluoromethyl-containing derivatives in good yields.

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