Synthesis of 7-trifluo[trichlo]romethyl-5-aryl[alkyl]-tetrazolo[1,5-*a*] pyrimidines in Ionic Liquid

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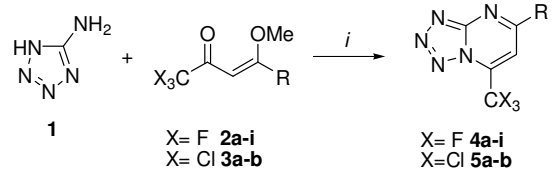
INTRODUCTION

Tetrazolopyrimidines are important biological agents with a wide range of pharmaceutical (e.g., hyperlipidemia, depression, glaucoma, and cardiac arrhythmias) and agrochemical uses.[1] The synthesis of this class of compounds by cyclocondensation reaction requires extreme conditions such as the use of acids, high temperatures, and prolonged reaction times. Another drawback for obtaining these compounds is the low yields. Furthermore, the synthesis of trifluoromethylated tetrazolopyrimidine from trifluoromethylated substrates is very limited.[2] The incorporation of fluorine into a drug allows simultaneous modulation of electronic, lipophilic, and steric parameters, all of which can critically influence both the pharmacodynamic and pharmacokinetic properties of drugs.[4]

In this work, we develop a simple and convenient protocol for the direct synthesis of 7-trifluo(trichlo)romethyl-5-aryl(alkyl)-tetrazolo[1,5-*a*]pyrimidine through cyclocondensation of 1,1,1-trifluo(trichlo)ro-4-methoxy-3-alken-2-ones and 5-aminotetrazole, using ionic liquid.

RESULTS AND DISCUSSION

The 7-trifluo(trichlo)romethyl-5-aryl(alkyl)-tetrazolo[1,5-a]pyrimidines **4a-i, 5a-b** were prepared from cyclocondensation reactions between 1,1,1-trifluo(trichlo)ro-4-methoxy-3-alken-2-ones **2a-i, 3a-b** (1.0 mmol) and 5-aminotetrazole **1** (1.0 mmol), in BMIM[BF_4] (1.0 mmol) and HCl (0.1 mmol), at 120°C, for 6 hours **(Figure 1)**. After the reaction time, the products were extracted with chloroform (5 mL), washed with water (3 x 5 mL), and then dried on magnesium sulfate.



i: BMIM[BF_4], 6h, 120°C, HCl (0,1%)

Figure 1. Synthesis of 7-trifluo(trichlo)romethyl-5-aryl(alkyl)-tetrazolo[1,5-a]pyrimidines **4a-i, 5a-b.**

The products were obtained at moderate to good yields in a pure form and without an additional purification step (**Table 1**). The structure of the 7-trifluo(trichlo)romethyl-5-aryl(alkyl)-tetrazolo[1,5-*a*]pyrimidines was determined by ^{1}H, ^{13}C, HMBC, and HMQC NMR spectroscopy, as well as by X-ray diffraction.

Table 1. Yields of 7-trifluo(trichlo)romethyl-5-aryl(alkyl)-tetrazolo[1,5-a]pyrimidines **4a-i, 5a-b.**

Product	R^1	yields(%)[a]
4a	Ph	80
4b	4-F-C_6H_4	97
4c	4-Br-C_6H_4	90
4d	4-I-C_6H_4	83
4e	4-Me-C_6H_4	80
4f	4-OMe-C_6H_4	89
4g	Tien-2-il	80
4h	Biphen-4-yl	95
4i	CH_3	73
5a	Ph	82
5b	CH_3	74

[a]Yield of isolated product.

CONCLUSION

In summary, our method succeeded in preparing novel 7-trifluo(trichlo)romethyl-5-aryl(alkyl)-tetrazolo[1,5-*a*]pyrimidines through a fast one-step and highly regioselective reaction, using starting materials synthetized in our laboratory. The method is practical and simple, and results in products with moderate to good yields.

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