Chemoselective fluorination of 2-hydroxy-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones using DAST

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INTRODUCTION

Multi-component reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention from the vantage point of combinatorial chemistry.[1] On the other hand, fluorine substitution can alter the chemical properties, disposition, and biological activity of drugs. Fluorine substitution can also have a profound effect on drug disposition, in terms of distribution, drug clearance, route(s), and extent of drug metabolism.[2] Such changes can be used constructively by medicinal chemists to improve both the safety and the efficacy of a drug.

Thus, considering the importance described and with base in works previously published by us,[3] the aim of this work is to report a facile, efficient and chemoselective fluorination of 2-hydroxy-2*H*-chromenones **1** using DAST (diethylaminosulfur trifluoride).

RESULTS AND DISCUSSION

In an attempt to evaluate the behavior of 2-hydroxy-2*H*-chromenones (**1a-e**) in the presence of DAST, we initially carried out reactions employing DAST in a 1:2 molar ratio (excess of the DAST), in dichloromethane as solvent, for 24 h at room temperature (Scheme 1). These reactions demonstrated that only a monofluorination reaction in the 2 position occurred (**2a-e**) with 100% of chemoselectivity and no other product was obtained. The products **2a-e** were easily isolated as solids by filtration and purified by a simple washing with cold ethanol, in good yields. Other conditions were tested with the goal of also promoting the difluorination reaction on the carbonyl functions present, however, under any condition, the presence of the difluorinated or dehydrated compounds was not observed.

CONCLUSION

In the present work, we have demonstrated that using a mild and efficient protocol for the chemoselective fluorination reaction of the 2-hydroxy-tetrahydro-2*H*-chromenones by DAST in CH_2Cl_2 at 0 - 25 °C for 24 hours, 2-fluoro-2*H*-chromenones can be easily obtained in good yields (63-81 %) and as an unique product, because no side reaction products were observed or isolated.

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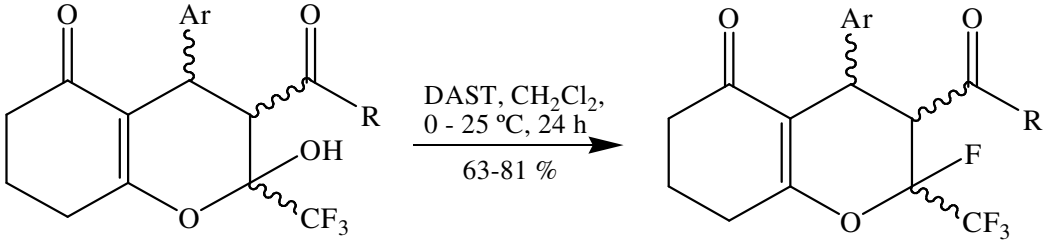

1a-e **2a-e**

1,2	a	b	c	d	e
Ar	Ph	Ph	Ph	Ph	4-ClPh
R	Ph	4-FPh	2-furyl	2-thienyl	2-thienyl

Scheme 1. Synthesis of 2-fluoro-2*H*-chromenones (2a-e)