Category

Synthesis of Heterocycles

Key words

trichloroisocyanuric acid

intramolecular cyclization

chromenones

H. XIANG, C. YANG* (SHANGHAI INSTITUTE OF MATERIA MEDICA, P. R. OF CHINA)

A Facile and General Approach to 3-[(Trifluoromethyl)thio]-4*H*-chromen-4-one

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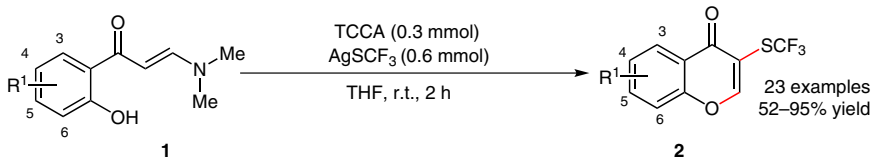
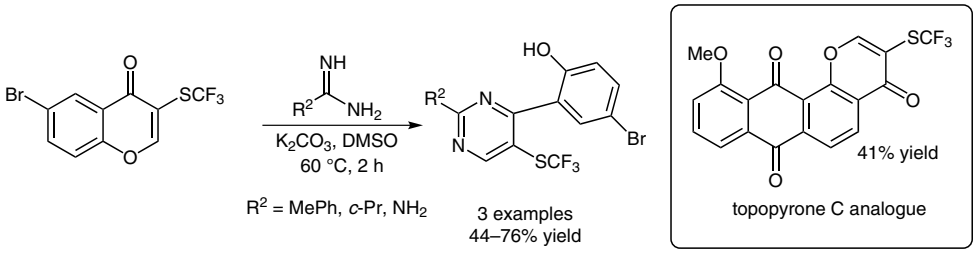
Direct Cyclization–Trifluoromethylthiolation to 4*H*-Chromen-4-ones



R^1 = 4-H, 4-Me, 4-Et, 4-Pr, 4-*i*-Pr, 4-OMe, 4-F, 4-Cl, 4-Br, 4-Ph, 4-(4'-$MeOC_6H_4$), 4-NO_2, 5-OMe, 5-Et, 5-Br, 5-Cl, 4,5-$(OMe)_2$, 4,5-Me_2, 4-Cl-5-Me, 4,6-Me_2, 4-Cl-6-Br, 4-(4'-MeO_2C-C_6H_4-), 4,5-$(CH{=}CH{-})_2$



Significance: Reported is a general synthesis of 3-[(trifluoromethyl)thio]-4*H*-chromen-4-ones **2** from 1-(2′-hydroxyphenyl)-3-dimethylaminoprop-2-enones **1** and the active electrophilic trifluoromethylthio moiety generated from $AgSCF_3$and trichloroisocyanuric acid (TCCA). This synthetic approach leads to the direct introduction of the SCF_3 group into chromen-4-ones, which represents a very desirable technique to produce diverse molecules for the medicinal chemist. The screening of reaction conditions showed that the reaction is highly dependent on the solvent; for example, yields in THF were better than in DMF; however, no product was obtained for reactions that were carried out in MeCN, CH_2Cl_2, DMSO, MTBE or toluene. The reaction also showed dependency on the optimized amount of TCCA (1.5 equiv), and remarkable insensitivity to air and moisture. The synthetic utility of this reaction to synthesize other SCF_3-containing heterocycles such as a topopyrone C analogue was also investigated.

Comment: The trifluoromethylthio group is incorporated in many bioactive molecules such as the hypotensive agents losartan and nifedipine (L. M. Yagupolskii et al. *J. Fluorine Chem*. **2001**, *109*, 87). Classic approaches of introducing this group include an indirect, multistep method (A. E. Feiring *J. Org. Chem*. **1979**, *44*, 2907). Herein, an easy and direct synthetic route was used to accomplish the same result. A mechanism was presented without evidence. It includes the possibility of an intramolecular Michael addition–cyclization of **1**, followed by enolate nucleophilic attack on the $^{+}SCF_3$ species, then a *N*,*N*-dimethylamine elimination process to produce **2**.

SYNFACTS Contributors: Victor Snieckus, Mona Gamal-Eldin (Snieckus Innovations)
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