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Short communication

Synthesis of 8-substituted 1,5-diazabicyclo[3.2.1]octane derivatives *via* double aza-Michael addition of homopiperazine to 3-trifluoroacetyl-4*H*-chromenes

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ABSTRACT

The reaction of homopiperazine with 2-trifluoroacetyl-1*H*-benzo[*f*]chromenes affords 2-(1,5-diazabicyclo[3.2.1]octan-8-yl)-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[*f*]chromen-3-ols, while 3-trifluoroacetyl-4*H*-chromenes give 2-[2-(1,5-diazabicyclo[3.2.1]octan-8-yl)ethyl]phenols. Both reactions are the first examples of synthesis of 1,5-diazabicyclo[3.2.1]octane core via double Michael addition and include cascade Michael addition/pyran ring opening/Michael addition.

1. Introduction

One of the strategic reactions for the formation of C—N bond is the aza-Michael reaction, which is widely used in the synthesis of agrochemicals, pharmaceuticals and fluorescent materials [1]. Using polyfunctional substrates, aza-Michael reaction may be the initial stage of the cascade process and lead to a significant increase in the molecular complexity. Promising objects for studying the processes of cyclization of Michael adducts are 3-trifluoroacetyl-4*H*-chromenes and their benzo-fused analogues, which can be easily obtained *via* cascade reactions of *ortho*-quinone methide precursors and 1,1,1-trifluoro-4-morpholinobut-3-en-2-one [2,3][2,3a]. The presence of an oxyvinyl moiety conjugated to the electron-withdrawing group makes 3-trifluoroacetyl-4*H*-chromenes masked 1,3-binucleophiles; it should be noted that highly electrophilic related β-ketoaldehydes are unstable compounds. At the same time, 3-acyl-4*H*-chromenes are stable and retain a high reactivity. The push-pull character of the double bond in the pyran ring opens up ample opportunities for obtaining a variety of heterocycles. In continuation of our interest in the chemistry of 3-trifluoroacetyl-4*H*-chromenes [3], we have studied their interaction with homopiperazine (1,4-diazepane) due to wide range of biological effects of their derivatives. Among substituted homopiperazines novel inhibitors of the CCR2b receptor [4a], gelatinase [4b], dipeptidyl peptidase IV [4][4c] and proteasomes [4d] were identified. In addition, some of them possess anti-cancer [4e] and anti-tubercular activity [4f].

2. Results and discussion

We have shown that stirring a mixture of homopiperazine **1** and 2-trifluoroacetyl-1*H*-benzo[*f*]chromenes **2a–c** in the molar ratio 1:1 in methanol affords 2-(1,5-diazabicyclo[3.2.1]octan-8-yl)-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[*f*]chromen-3-ols **3a–c** (Scheme 1).

^{13}C NMR spectra of compounds **3a–c** show the carbon atom of trifluoromethyl group and the adjacent hemiacetal carbon atom as quartets at 122.9 ppm with $^{1}J_{C–F}$ = 288 Hz and at 96.5–96.7 ppm with $^{2}J_{C–F}$ = 31.5 Hz, respectively. The carbon atoms connected with two nitrogen atoms ($C^{8'}$) resonate at 88.0 ppm. The signals for the benzylic carbon atoms (C^{1}) in the ^{13}C NMR spectra are found at 21.5–21.6 ppm. The proton of the hydroxyl group in **3a–c** is strongly deshielded (δ = 12.24–12.27 ppm in $CDCl_3$ solution), which is due to the presence of a strong intramolecular hydrogen bond with the nitrogen atom. Chemical non-equivalence of the carbon atoms $C^{4'}$ and $C^{2'}$, $C^{6'}$ and $C^{7'}$ is also explained by the hydrogen bond. Characteristic signals in the ^{1}H NMR spectra corresponding to proton H^{2} are observed at 2.26–2.28 ppm as a doublet of doublets with ^{3}J = 10.8–11.0 and ^{3}J = 6.3–6.4 Hz due to vicinal interaction with protons $H^{8'}$ and H^{1}, respectively. The protons $H^{8'}$ are displayed as a doublet at 3.99–4.03 ppm. The number of protons that are directly linked to ^{13}C atoms, inferred from DEPT spectra, is in

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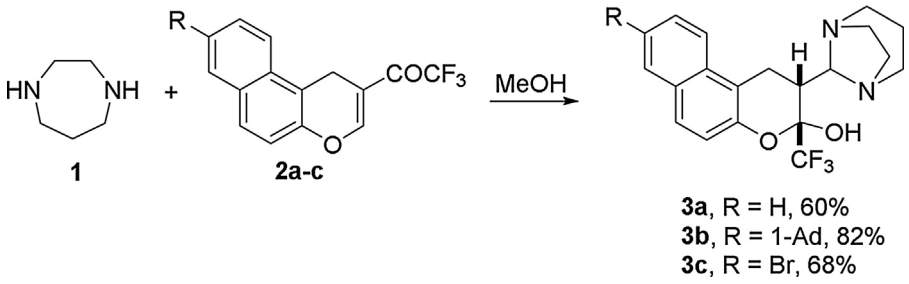


Scheme 1. Reaction of homopiperazine and 2-trifluoroacetyl-1*H*-benzo[*f*]chromenes.

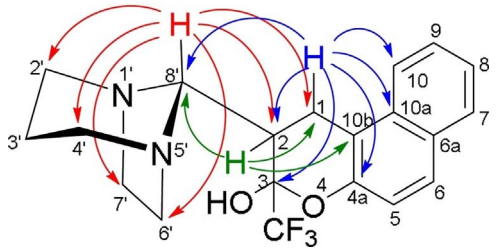
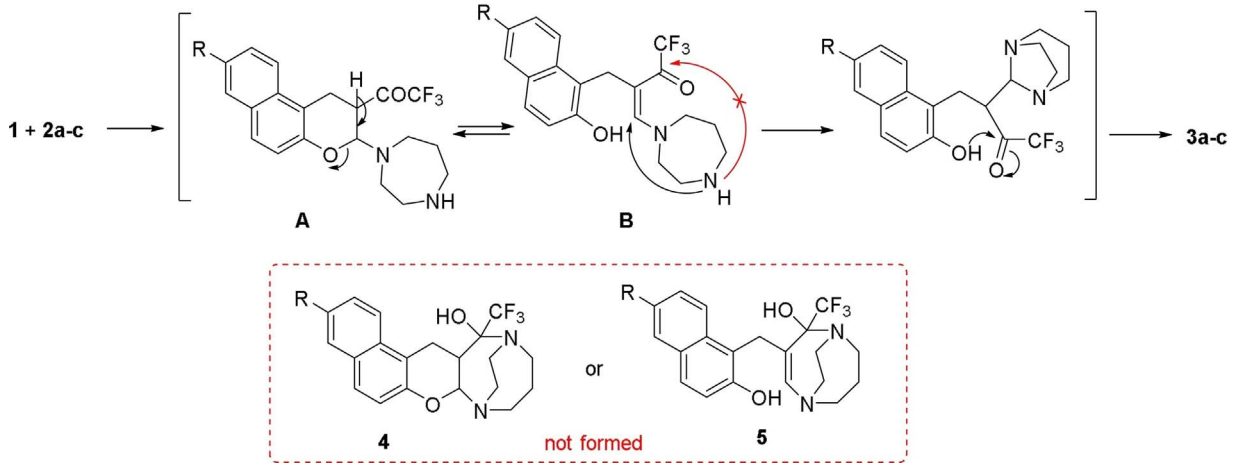


Fig. 1. Selected HMBC $^{1}H–^{13}C$ correlations of compound **3a.**

accordance with the presented structures. The $H^{8'}$ proton shows heteronuclear correlations with five methylene carbon atoms, including the benzyl carbon atom C^{1} (in the HMBC spectrum of **3a**, Fig. 1), which denies the structures of isomeric cyclic hemiaminals **4** and **5** (Scheme 2).

This cascade reaction includes the following main steps: aza-Michael addition of homopiperazine to chromenes **2**, opening of the dihydropyran ring in the intermediate **A** with formation of the enaminone **B**, repeated aza-Michael addition and hemiketalization (Scheme 2).

Additionally, the *cis*-position of 1,5-diazabicyclo[3.2.1]octane fragment and hydroxyl group in the structure of compound **3a** was confirmed by X-ray diffraction analysis of monocrystal (Fig. 2). The unit



Scheme 2. Plausible mechanism of formation of compounds **3a-c**.

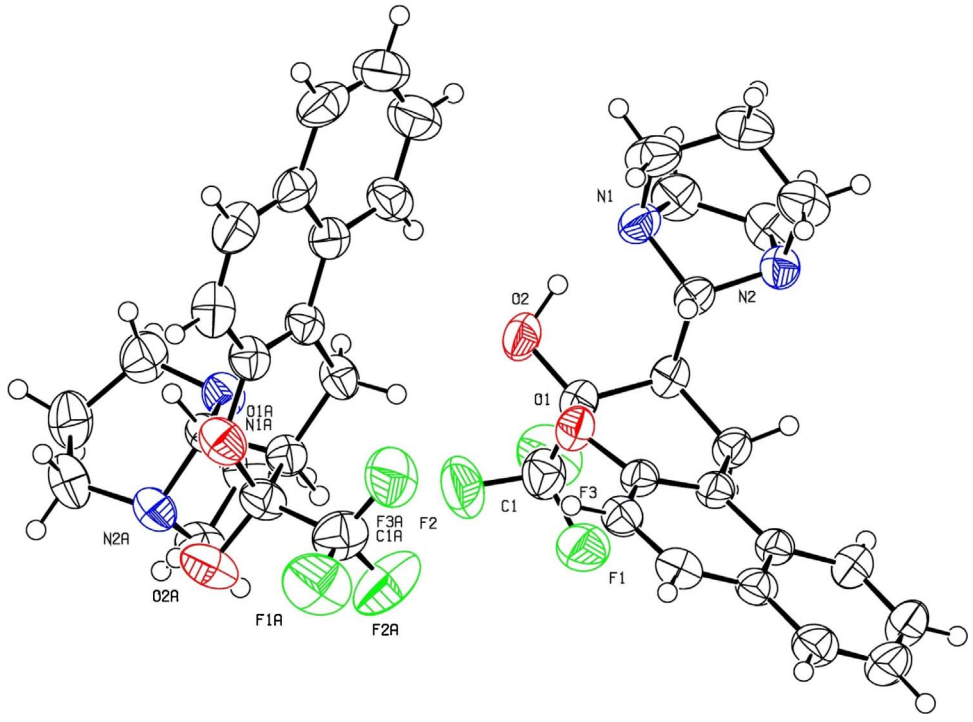


Fig. 2. An ORTEP diagram of compound **3a** with 50% probability ellipsoid displacement.