Reactions of 5,7-dimethyl-2-polyfluoroalkyl-8-azachromones with N-nucleophiles

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On treatment with ammonia, primary amines, and pyrrolidine, 5,7-dimethyl-2-trifluoromethyl-8-azachromone undergoes ring opening to give β-aminovinyl ketones. The reactions with morpholine and piperidine proceed as addition to give 2-morpholino- and 2-piperidino-8-azachromanes. With ethylenediamine, diethylenetriamines, hydrazine hydrate, and hydroxylamine, this compound reacts similarly to 2-polyfluoroalkylchromones, yielding CF3-containing dihydrazides, pyrazoles, and isoxazoles with a 2-pyridone substituent.

Key words: 5,7-dimethyl-2-polyfluoroalkyl-8-azachromones, 5,7-dimethyl-2-polyfluoroalkylchromones, amines, hydrazine hydrate, hydroxylamine, β-aminovinyl ketones, 2,3-dihydro-1H-1,4-diazepines, pyrazoles, isoxazoles.

The reactions of chromones with nucleophilic reagents are known to involve mainly the C(2) atom, irrespective of the presence and the nature of the substituent at this atom. The introduction of a polyfluoroalkyl group into position 2 of the chromone system appreciably increases the reactivity of the pyrone ring and makes 2-polyfluoroalkylchromones highly reactive substrates in 1,4-nucleophilic addition reactions. Previously, we studied the reactions of these compounds with various amines, hydrazines, hydroxylamine, and sodium azide, which furnished a broad range of R– containing nitrogen heterocycles. It was noted that electron-withdrawing substituents in the benzene ring promote the attack of an amine molecule on the C(2) atom, which can either stop after the nucleophilic addition or proceed further with opening of the pyrone ring to give β-aminovinyl ketones (AVK). Therefore, it appeared of interest to compare the reactivity of 5,7-dimethyl-2-polyfluoroalkylchromones10 and 2,5,7-trimethyl-8-azachromone11 with the reactivity of 5,7-dimethyl-2-polyfluoroalkyl-8-azachromanes (5,7-dimethyl-2-polyfluoroalkyl-4H-pyrano[2,3-b]pyridin-4-ones), obtained by condensation of 3-acetyl-4,6-dimethyl-2-pyridone with R=CF3, CF2H, (CF3)2H in the presence of LiH.12

Results and Discussion

We have studied the reactions of 5,7-dimethyl-2-trifluoromethyl-8-azachromone (1) with various N-nucleophiles and compared its behavior in these reactions with the behavior of 5,7-dimethyl-2-trifluoromethylchromone (2) and 2,5,7-trimethyl-8-azachromone (3). This allowed us to elucidate the influence of the N(8) atom and the CF3 group on the reactivity of the chromone system. As expected, azachromone (1) readily reacts with ammonia, primary mono-, di-, and triamines, secondary cyclic amines, hydrazine hydrate, and hydroxylamine. These reactions involve the C(2) atom and give diverse 4,6-dimethyl-2-pyridone derivatives (the 2-pyridone form predominates in the tautomeric equilibrium with the 2-hydroxyipyridine form11,13).

Previously, it has been shown that the interaction of chromone 2 with ammonia and methyl- and benzylamines in an alcohol solution at –20 °C stops after 1,4-addition giving rise to 2-aminochromanes 4a–c. We found that chromone 2 also easily adds 2-aminooethanol to give compound 4d but does not react with aniline. Unlike chromone 2, azachromone 1 reacts with ammonia and primary amines at –20 °C or with aniline in the presence of Et3N at 75 °C with pyrrole ring opening to give AVK 5a–e (Scheme 1). The reaction with aniline is the second known example in which the chromone system reacts with aromatic amines at the C(2) atom (previously, we reported a similar reaction of 6-nitro-2-trifluoromethylchromone).

The different structure of the products obtained in reactions of chromones 2 and 1 with primary amines is, apparently, related to the formation of a stable 2-pyridone fragment in the latter case, which shifts the ring—chain tautomeric equilibrium toward the open form 5. The replacement of the trifluoromethyl group by a methyl group does not prevent the reaction of azachromone 3 with methyl- and benzylamines at –20 °C, which also follows a route with pyrrole ring opening in AVK 5f,g. However, in

the reaction with NH₃, azachromone 3 is recovered unchanged. Judging by the chemical shift of the proton attached to the nitrogen atom (δ_{NH} = 10.4—11.5 for 5b,c,g in CDCl₃), compounds 5a—g have a Z-configuration of the double bond and occur as s-conformers stabilized by an intramolecular hydrogen bond (IMHB). The CF₃ group in 5c deshields the vinylic proton of the aminoenone system compared with the Me group in 5g; hence, its signal is shifted downfield by 0.58 ppm.

2-Difluoromethyl-5,7-dimethylchromone (6), like chromone 2, adds benzylamine to afford chromanone 4e, whereas 5,7-dimethyl-2-(1,1,2,2-tetrafluoroethyl)chromone (7) does not react with benzylamine, 2-aminoethanol, or ammonia under similar conditions (Scheme 2). Thus, primary amines open the pyrone ring in 5,7-dimethyl-8-azachromones, irrespective of the nature of the substituent at the C(2) atom, whereas the reactions of RNH₂ (R = H, Alk) with 5,7-dimethyl-2-RF-chromones stop after nucleophilic 1,4-addition and are fairly sensitive to the steric factor.

Diethylamine does not react with chromones 1—3, while secondary cyclic amines (morpholine, piperidine) do not react with chromones 2 or 3, but add to the double bond of azachromone 1 in a THF solution at ~20 °C to give azachromanones 8a,b, which proved to be more stable than 2-piperidino- and 2-morpholinochromanes, prepared previously from 2-trifluoromethylchromones containing a nitro group in the benzene ring. Indeed, the piperidine derivative 8b starts to decompose into the initial substances after storage for several months, whereas a similar adduct of piperidine with 2-trifluoromethylchromone, after storage for several days. The formation of chromanones 8a,b attests to a more electrophilic nature of the C(2) atom in azachromone 1 with respect to that in chromone 2 (on passing from 2 to 1, the chemical shifts of the C(2)—C(4) atoms in the ¹³C NMR spectra shift downfield by 0.52—0.54 ppm).

The reaction of azachromone 1 with pyrrolidine carried out under the same conditions gave unexpectedly the Z-isomer of AVK 5h (Scheme 3), i.e., transition from a six- to a five-membered ring is accompanied by an in-