Synthesis of 3-alkylamino-3-(2-hydroxyaryl)-1-polyfluoroalkylprop-2-en-1-ones and 2-polyfluoroalkyl-4H-chromen-4-imines

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Condensation of Schiff’s bases (prepared from 2-hydroxy- or 2-hydroxy-5-methylaceto-phenones and primary amines) with ethyl polyfluoroalkanoates in the presence of LiH in THF affords 3-alkylamino-3-(2-hydroxyaryl)-1-polyfluoroalkylprop-2-en-1-ones, which undergo cyclization in acidic media into 2-polyfluoroalkyl-4H-chromen-4-iminium salts. When neutralized with aqueous ammonia, the latter give 2-polyfluoroalkyl-4H-chromen-4-imines in high yields.

Key words: Schiff’s bases, polyfluoroalkanoic acid esters, amino enones, 2-polyfluoroalkyl-4H-chromen-4-imines and their salts.

Chromones (4H-chromen-4-ones) represent an important class of oxygen-containing heterocyclic moieties of flavonoids, which are abundant plant constituents. Many chromone derivatives have been thoroughly studied and found wide use as drugs. However, data on the synthesis and chemical properties of 4H-chromen-4-ylideneamines (4H-chromen-4-imines) are scarce. Earlier, it was shown that Schiff’s bases prepared from 2-hydroxyacetophenone and alkylamines react with arenecarboxylates in the presence of Pr₄NF to give 3-alkylamino-3-(2-hydroxyphenyl)-1-arylprop-2-en-1-ones, which undergo cyclization into N-substituted 2-aryl-4H-chromen-4-imines when heated with AcOH in aqueous THF. In addition, alkyl methyl ketimines were known to react with alkyl trifluoroacetates under analogous conditions to give 3-alkyl-3-alkylamino-1-trifluoromethylprop-2-en-1-ones. Based on these data, we recently obtained for the first time 2-trifluoromethyl-4H-chromen-4-imines by condensation of 2-hydroxyacetophenone imines with ethyl trifluoroacetate via intermediate 3-alkylamino-3-(2-hydroxyphenyl)-1-trifluoromethylprop-2-en-1-ones. In acidic media, these compounds are more reactive with respect to N- and C-nucleophiles than en-1-ones. In acidic media, these compounds are more amino-3-(2-hydroxyphenyl)-1-trifluoromethylprop-2-en-1-ones with ethyl trifluoroacetate 4-imines by condensation of 2-hydroxyacetophenone imino N atom even in the presence of AcOH to generate iminium cations with the enhanced electrophilicity of the C(2) atom, which is usually attacked first in the reaction of a chromone system with nucleophiles. In most cases, the latter circumstance makes it impossible to directly convert chromones into chromenimines, except for the reactions of 2-RF-chromones with 2-aminoethanol for R²F = (CF₂)₂H and C₂F₅, which involves the carbonyl group to give the corresponding imines. The present study is devoted to the reactions of Schiff’s bases prepared from 2-hydroxy- and 2-hydroxy-5-methylaceto-phenones with ethyl polyfluoroalkanoates and aimed at developing a general route to 2-polyfluoroalkyl-4H-chromen-4-imines, which are of interest as promising and highly reactive substrates for the synthesis of various polyfluoroalkyl-containing heterocyclic compounds.

Results and Discussion

Ketimines 1a—e were obtained in 58—94% yields by the reactions of benzylamine, isopropylamine, and 2-aminoethanol with 2-hydroxy- and 2-hydroxy-5-methylaceto-phenones. Primary amines were reported to easily react with aromatic aldehydes and ketones containing an ortho-OH group, probably because of thermodynamic stabilization of reaction products by a strong intramolecular hydrogen bond (IMHB) with the azomethine N atom. We found that the condensation of imines 1a—e with CF₃CO₂Et and H(CF₂)CO₂Et in the presence of LiH in boiling THF affords amino enones 2a—e and 2f—i in 51—82% and 11—38% yields, respectively. The use of ethyl difluoroacetate and ethyl trichloroacetics under analogous conditions leads to resification. Treatment of compounds 2a—i with ethanolic HCl at ≈20°C for 2 h gives chromeniminium chlorides 3a—i; salt 3e was isolated and characterized as a monohydrate. Neutraliza-
tion of aqueous solutions of hydrochlorides 3a–i with ammonia affords chromenimines 4a–i in 63–91% yields (Scheme 1).

Scheme 1

In some cases, the crude products contained admixtures of amino enones 2, which are insoluble in hot hexane and thus can easily be separated from the target chromenimines 4. To answer the question as to whether this impurity is the non-consumed amino enone 2 or it is produced by the base-catalyzed competitive opening of the pyrone ring in chromeniminium cation 3, we studied the hydrolysis of trifluoromethylated compounds 2a, b, d and 4a, b, d under various conditions. It turned out that treatment of chromenimines 4 with aqueous AcOH at ≈20 °C for 12 h (or at 80 °C for 1 h) gives chromanones 5, which were also obtained from compounds 2 under analogous conditions. However, treatment of compounds 4 with aqueous AcOH and AcONH4 results in fast formation of amino enones 2. Therefore, during the isolation of compounds 4 from solutions of their salts, neutralization is accompanied by side opening of the pyrone ring, which accounts for the presence of 2 as an impurity. To minimize the probability of this undesired reaction, ammonia should be used in a slight excess and added in one portion, because chromenimines 4 are fairly stable in basic media.

The data obtained suggest that the interconversions of compounds 2 and 4 and their hydrolysis to chromanones 5 proceed via the same intermediate A, while further con-

versions of the latter mainly depend on pH (Scheme 2). Apparently, the rapid conversion 4 → 2 involves the open enaminoiminium cation B since enaminoimines themselves are easily hydrolyzed to amino enones with the γ-arrangement of the RHN- and trihalogenomethyl groups11 as in compounds 2. Note also that enaminoketones 2 containing no ortho-OH group are resistant to hydrolysis, whereas their regioisomers with the α-arrangement of the RHN- and RF groups are hydrolyzed to β-diketones under mild conditions.5 The pyrone ring of 2-trifluoromethylchromones easily undergoes opening in the presence of NH3,12 but does not add water at the activated C=C bond; i.e., 2-trifluoromethylchromen-4-imines are actually more reactive than 2-trifluoromethylchromones in acidic media and hence are attractive building blocks for the synthesis of various trifluoromethylated heterocyclic compounds.

Scheme 2

Recently,13 the condensation of khellinone (5-acetyl-6-hydroxy-4,7-dimethoxybenzo[b]furan) with CF3CO2Et