Fluoro-containing Heterocycles: V. * Cyclization of 3-Azolylamino-2-polyfluorobenzoylacrylates**

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Abstract—The heating of ethyl 3-azolylamino-2-polyfluorobenzoylacrylates in acetonitrile in the presence of KF gave rise to derivatives of 1-azolyl-substituted quinolones or azolo[1,5-alpyrimidines.

In our preceding studies we extensively used cyclization of 3-hydrazido derivatives of 2-polyfluoro-benzoylacrylic acids in the synthesis of [i,j]-annealed quinolone carboxylic acids [2, 3] (Scheme 1). In these tricyclic systems the quinolone carcass is anneled with six-membered oxadiazine or thiadiazine rings, and they may be regarded as analogs of the known antibacterial agents, ofloxacin and marbofloxacin.

Scheme 1.

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Scheme 2.

The other methods of synthesis of [i,j]-fused fluoroquinolones are also known [4]; however in the literature are hardly mentioned cases of a five-membered cycles anneled at facets [i,j] of a quinolone carcass. A single example concerns a preparation of derivatives of pyrrolo[3,2,1-i,j]quinoline-5-carboxylic acid by building up of a pyridone fragment (Scheme 2) [5].

Proceeding from the data of the previous research [2, 3, 6] we presumed that the reaction between 2-aminazoles IIa, b with ethyl 2-polyfluorobenzoyl-3-ethoxyacrylates (Ia, b) can provide derivatives of 1-azolylsubstituted quinolones IV capable of further cyclization into tetracyclic compounds V.

Actually we succeeded in carrying out the first part of the scheme. The reaction of compounds Ia, b and IIa, b in ethanol at 18–20°C gave rise to 3-azolylamino-2-polyfluorobenzoylacrylates (IIIa–d) (Scheme 3). The structure of these compounds was confirmed with 1H NMR spectra. For instance, same as initial acrylate Ia compound IIIa in solution exists as two geometrical isomers with respect to the C2–C3 bond as shows the presence in the 1H NMR spectrum of a double set of proton signals from the ester group, =CH–NH fragment, and from pyrazole and tetrafluorobenzoyl substituents.

Cyclization of acrylates III was carried out in boiling acetonitrile in the presence of KF within 2–4 h. We found that depending on the substituents X and Y the reaction occurs along different pathways. In cyclization of ethyl 2-pentafluorobenzoyl-3(pyrazol-3-yl)-aminoacrylate (IIIb) was obtained 1-substituted...
Scheme 3.

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\begin{array}{cccc}
\text{Ia, b} & \text{IIa, b} \\
& \text{H}_2N\text{N}=N \\
\text{IIIa–d} & \text{IVb} & \text{V} \\
\text{VI} & \text{VIIa, b} & \text{VIIIa–c} \\
\end{array}
\]

I. Y = H (a), F (b); II, VI, VII, X = CH (a), N (b); III, X = CH, Y = H (a), F (b); X = N, Y = H (c), F (d); VIII, NR₂ = pyrrolidin-1-yl, X = CH (a), N (b); NR₂ = morpholino, X = N (c).

The cyclization of quinolone IVb. In the mass spectrum of compound IVb is present a molecular peak with \( m/z \) 355 and also a strong peak (100%) corresponding to an ion [\( M-\text{COOC}_2\text{H}_4 \)]⁺. In the IR spectrum of compound IVb appear absorption bands at 1730 and 1640 cm⁻¹ of the stretching vibrations from carbonyls in the ester group and quinolone fragment respectively. In the \( ^{19}\text{F} \) NMR spectrum are observed the signals from four fluorine atom; therewith the chemical shifts, multiplicity of signals, and coupling constants are similar to those in the \( ^{19}\text{F} \) NMR spectra of the other derivatives of 1,4-dihydro-4-oxo-5,6,7,8-tetrafluoroquinoline-3-carboxylic acid that we have prepared before [2]. The \( ^1\text{H} \) NMR spectrum is consistent with the structure IVb, and in distinction from the initial acrylate IIIb the doublet of NH group is lacking, and the signal of the CH = proton appears as a singlet.

The attempt to perform further cyclization of compound IVb with the use of a stronger agent for binding HF, diazabicycloundec-7-ene (DBU), failed. Note that in the mass spectrum of compound IVb the ion peak [\( M-\text{HF} \)]⁺ is lacking; this peak usually is present among fragment peaks of compounds prone to further cyclization [2, 6]. The difficulty in performing the desired cyclization are probably due to the high strain in the fused system V.

It is interesting that the cyclization of tetrafluorobenzoyl analog IIIa occurs in dissimilar way: here forms not a quinolone structure of IV type but a derivative of pyrazolo[1,5-a]pyrimidine (VIIa). The structure of the latter was proved by \( ^1\text{H} \) and \( ^{19}\text{F} \) NMR spectra. In the mass spectrum of compound VIIa is present a peak of the molecular ion \( m/z \) 339, in the \( ^{19}\text{F} \) NMR spectrum appear signals from four fluorine atoms. In the IR spectrum of the compound in the C = O vibrations region is observed a single band from the ester group at 1725 cm⁻¹. Unlike the initial acrylate IIIa, compound VIIa in the \( ^1\text{H} \) NMR spectrum has no signals from two NH groups, and the characteristic multiplet belonging to the proton of the polyfluorobenzene fragment corresponds to the coupling thereof with four fluorine atoms of the ring. Thus all data indicate that in the concurrent reaction with the participation of a carbonyl group forms compound VIIa.

The cyclization of ethyl 2-tetrafluorobenzoyl-3-(1,2,4-triazol-3-yl)aminoacrylate (IIIc) takes a