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Synthesis of polyfluorinated 4-phenyl-3,4-dihydroquinolin-2-ones and quinolin-2-ones via superacidic activation of *N*-(polyfluorophenyl)cinnamamides

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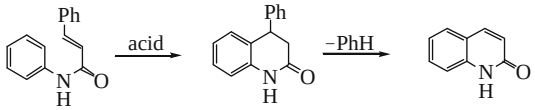
ABSTRACT

The cyclization reactions of a series of polyfluorocinnamanilides in triflic acid (CF_3SO_3H) yield 4-phenyl-3,4-dihydroquinolin-2-ones, which include a polyfluorinated benzene moiety as a part of the quinoline scaffold. These compounds undergo dehydrophenylation in the presence of $AlCl_3$ to give the corresponding polyfluoroquinolin-2-ones which are converted into polyfluorinated 2-chloroquinolines on treatment with $POCl_3$. A mechanism for the cyclization reaction presuming the intermediacy of a superelectrophilic O,C-diprotonated form of the starting material is suggested.

Benzoazaheterocycles containing fluorine atoms in the carbocyclic moiety possess diverse biological activities and are currently of significant interest.[1,2] For example, (poly)fluoroquinolin-4-ones have proved to be effective antimicrobial[3–9] and anti-AIDS[10] drugs, whereas several mono- and difluoroquinolin-2-ones are active against bacterial infections which are resistant to other types of medicines.[11–14] In this respect it is noteworthy that there is only scant data on quinolin-2-ones containing a polyfluorinated benzene ring. As a rare exception, only 6,7,8-trifluoroquinolin-2-one (prepared by hydrodechlorination of 4-chloro-6,7,8-trifluoroquinolin-2-one on a palladium catalyst) is described.[12]

As exemplified in Scheme 1, an efficient route to nonfluorinated quinolin-2-ones is based on the cyclization of cinnamanilides under the action of strong acids and superacids,[11,15–21] as well as of solid acids such as HUSY-zeolites and sulfated zirconia,[22] to give 4-phenyl-3,4-dihydroquinolin-2-ones which is followed by dehydrophenylation to yield quinolin-2-ones. The reaction cannot always be stopped at the first stage, as is highly desirable in view of the biological activity of 4-phenyl-3,4-dihydroquinolin-2-ones.[23] However, this is possible when polyphosphoric acid at elevated temperature,[19] triflic acid (CF_3SO_3H) at room temperature[20] or solid acids are used.[22]

Following this approach, several monofluoro-4-phenyl-3,4-dihydroquinolin-2-ones[15,16] and difluoroquinolin-2-ones have been prepared.[11,14] However, in our case, we were interested in other fluorinated quinolin-2-ones and, in a broad sense, quinolines. Until now, both types of compounds have been difficult to obtain due to the poor accessibility of their respective precursors including polyfluorinated arylamines without *ortho* substituents. Fortunately, relatively simple methods of selective hydrodehalogenation of perfluoroarenes, and particularly *ortho*-hydrodefluorination of readily available *N*-acetylpolyfluoroarylamines using zinc in aqueous ammonia have been developed recently.[24–26] Importantly, the same method allows selective hydrodechlorination of polyfluorochloroarylamines without their prior transformation into *N*-acetyl derivatives.[27] As a result, the opportunity to produce polyfluoroquinolines according to Scheme 1 is fundamentally increased. Nevertheless, the ability to achieve electrophilic cyclization of polyhalogenated cinnamanilides was still questionable taking into account the deactivating effect of polyhalogenation.



Scheme 1.

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Based on this background, a study of the cyclization of the 2,3,4,5-tetrafluoro- (**1a**), 2,4,5-trifluoro- (**1b**), 2,3,5-trifluoro- (**1c**), 4-X-3,5-difluoro- (X = H **1d**, Br **1e**, I **1f**) anilides of cinnamic acid to the corresponding fluorinated 4-phenyl-3,4-dihydroquinoline-2-ones **2** and subsequent dehydrophenylation to quinolin-2-ones **3** is reported.

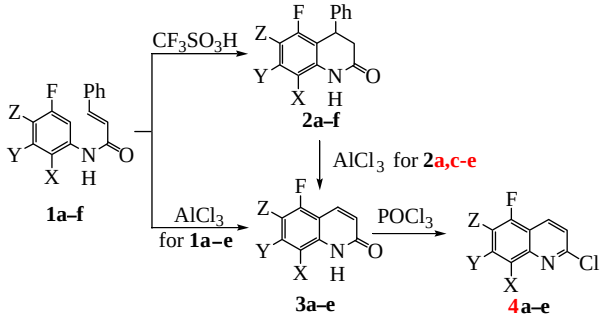
Cinnamanilides **1a–f** were obtained in 70–82% yields by reaction of cinnamoyl chloride with the corresponding polyfluoroanilines in aqueous acetone/K_2CO_3 according to the reported procedure[28] (see Supplementary data).

The transformations of **1a–f** into the target products **2a–f** and **3a–f** are shown in Scheme 2. Cyclization of **1a** in CF_3SO_3H was accomplished in 24 h at room temperature to give 5,6,7,8-tetrafluoro-4-phenyl-3,4-dihydroquinolin-2-one (**2a**) in 84% yield, whereas **1b** gave 5,6,8-trifluoro-4-phenyl-3,4-dihydroquinolin-2-one (**2b**) in 70% yield in three days. Increasing the reaction time did not improve the yields of **2a** and **2b** because of secondary reactions. In contrast, compounds **1c–f** were converted into the corresponding phenyldihydroquinolin-2-ones **2c–f** in good yields (90−95%) in 24 h.

Following the originally suggested mechanism of cyclization for nonfluorinated anilides **1**,[20] it can be assumed that compounds **1a–f** react through the intermediacy of superelectrophilic[29] dications **5** formed by O,C-diprotonation according to Scheme 3.[30]

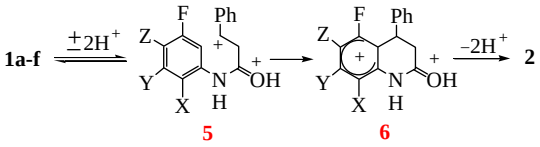
Substituents Z, X and Y could influence both the equilibrium concentration of dications **5** and the energy of the cyclization transition state. The latter, to some extent, is structurally similar to intermediates **6**. The comparatively poor reactivity of **1a** and **1b** compared with that of the other cinnamanilides can be explained both by the lower concentration of the corresponding dications **5** owing to the *−I* effect of Z, X = F and by the decreased stability of **6** due to the sufficiently strong *−I* effect of the fluorine atoms *meta* to the position attacked by the electrophile.

In accord with known data for nonfluorinated **2**,[20] compounds **2a–f** do not undergo elimination of benzene in triflic acid. In fact, reaction **2**→**3** requires a stronger acid and harsher conditions, for example, a large molar excess of $AlCl_3$ at >100 °C.[15–21] On the other hand, dehydrophenylation of products **2a–f** might suffer from substitution of fluorine by chlorine under the action of $AlCl_3$ at elevated temperature.[11,17] Nevertheless, it turned out that dihydroquinolin-2-ones **2a** and **2c**,**d** reacted smoothly at 110–160 °C to give quinolin-2-ones **3a** and **3c**,**d**, respectively, in 95–98% isolated yields (Scheme 2). Reaction of **2f** with $AlCl_3$ (110–115 °C) was complicated giving a 1:3 mixture of **3f** and **3d** resulting from the partial hydrodeiodination of **2f** and/or **3f**. Taking this into account, the reaction of the bromo compound **2e** with $AlCl_3$ was carried out under milder conditions (95–100 °C) and this provided a mixture of **3e** and **3d** in a 9:1 ratio.



a X = Y = Z = F; **b** X = Z = F, Y = H; **c** X = Y = F, Z = H; **d** X = Z = H, Y = F; **e** X = H, Y = F, Z = Br; **f** X = H, Y = F, Z = I

Scheme 2.



Scheme 3.

It seemed expedient to also study the direct conversion of anilides **1a–f** into quinolin-2-ones **3a–f** in the presence of $AlCl_3$. We found that reaction of **1b–e** with $AlCl_3$ at 100–160 °C provided compounds **3b–e** in good yields (Scheme 2), although the reaction of **1a** with $AlCl_3$ carried out at 120–125 °C and 155–160 °C led to complex mixtures, containing only ~40% and ~60% of **3a**, respectively.

The successful synthesis of quinolinones **3a–e** opens the opportunity to synthesize a large variety of their derivatives, particularly products of their nucleophilic functionalization at both the carbocyclic and the heterocyclic moieties. As an example, reactions of compounds **3a–e** with $POCl_3$ gave 2-chloroquinolines **4a–e** in 61–73% yields (Scheme 2) which are expected to serve as versatile starting materials for preparing 2-functionalized polyfluoroquinolines.

In conclusion, we have developed an efficient synthesis of 4-phenyl-3,4-dihydroquinolin-2-ones, quinolin-2-ones and 2-chloroquinolines with a polyfluorinated carbocyclic moiety based on superacidic activation and electrophilic cyclization of the corresponding polyfluorinated anilides of cinnamic acid.

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Supplementary data

Supplementary data (complete experimental and spectroscopic data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.013.

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