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Reactions of Acetoacetates With Electron-deficient Anilines

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Received: #00th #00 2007

Contents:

1. [Abstract](#)
2. [Introduction](#)
3. [Synthesis of Acetanilides and Azomethines](#)
4. [Ring Closure Reactions](#)
5. [Experimental](#)
6. [Acknowledgement](#)
7. [References](#)

Abstract

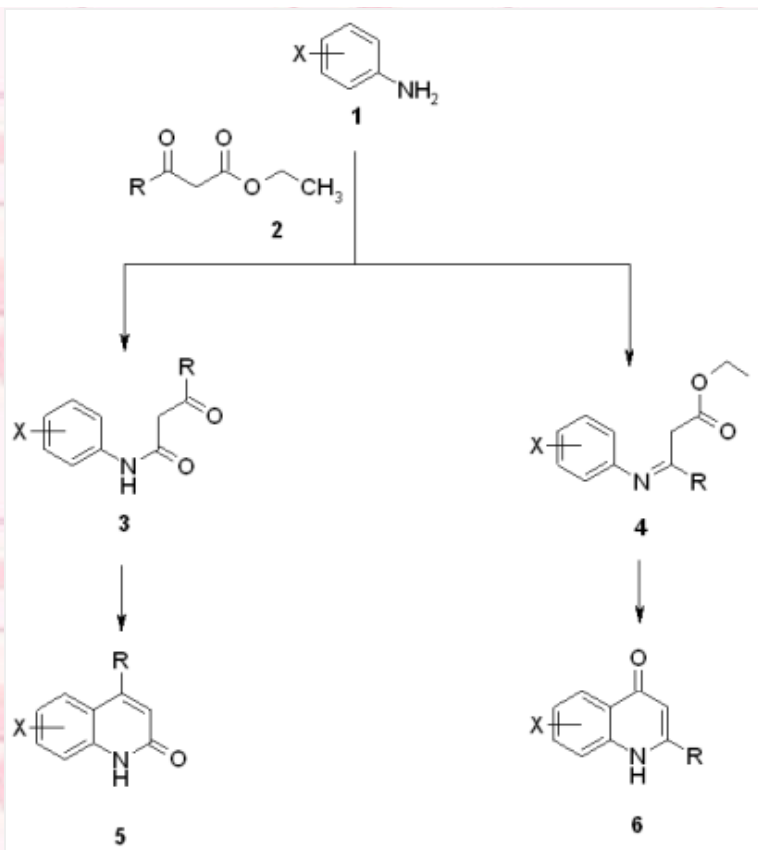
The reaction of anilines, having electron-withdrawing substituents such as chloro- or trifluoromethyl groups, with acetoacetates was studied. Using the "watering protocol" [5], mainly acetanilides were obtained which were intended to cyclize to 2-quinolones. However, in contrast to electron-rich anilides, it was not possible to obtain cyclized products from electron-deficient anilides.

Introduction

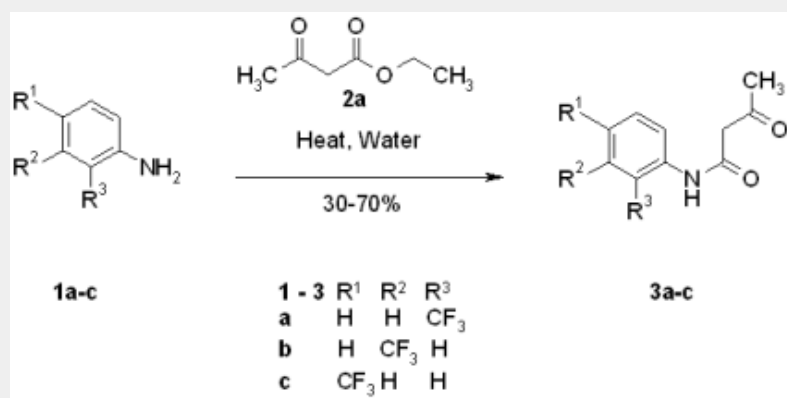
4- And 2-trifluoromethyl quinolone derivatives (**5**, **6**; R = CF₃) are useful intermediates and their synthesis and reactions were studied in the last years extensively [1-8]. The synthesis from anilines **1** and acetoacetates **2** gives in the first step isomeric acetanilides **3** or azomethines **4**, depending on the reaction conditions and substituents, which cyclize then in a further step, a reaction type known as Konrad-Limpach or as Knorr synthesis [9, 10].

We have shown that 4-trifluoromethyl-2-quinolones **5** with suitable substituents either in the aromatic or in the heteroaromatic ring (e.g. X = 6- and 7-OMe) show excellent fluorescence properties [1] which can be used as fluorescence markers for biological polymers such as proteins or amino-carbohydrates [3, 4].

Anilines **1** with electron donating substituents such as methoxy- or amino groups give excellent yields in the condensation and subsequent ring closure to both 2- and 4-quinolones **5**, **6** (R = CF₃) [1-4, 8]. Less reactive anilines with halogen substituents were investigated by several workgroups [5-7] and some success was obtained by dedicated reaction conditions ("watering protocol" of the Schlosser group [5] or temperature and catalyst control [7]).

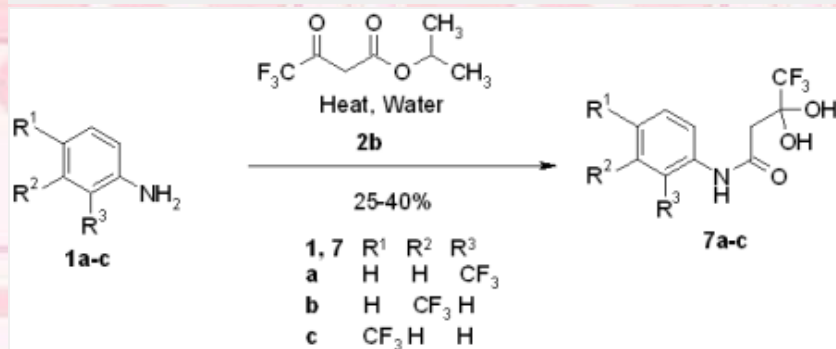


Synthesis of Acetoacetanilides and Azomethines



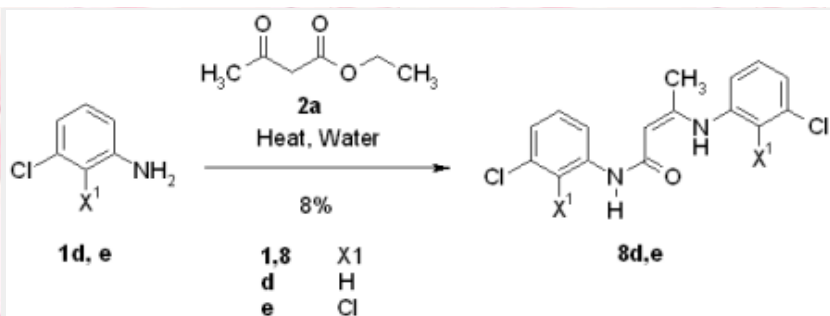
For further studies of fluorescence properties we started a synthesis project which should lead from trifluoromethyl or dichloro substituted anilines to the corresponding quinolones. Among the reported syntheses, only by the "watering protocol" of the Schlosser group [5] fluoro, chloro, bromo and iodo derivatives were obtained. Other syntheses were restricted to fluoro derivatives only [7]. By Schlosser's watering protocol, the 2-quinolone derivatives should be favored.

We performed the reactions from anilines **1a-c** having trifluoromethyl groups as substituents in 2-,3- and 4-position, with acetoacetate **2a** (R = Me) without solvent by heating to 130 °C for some hours and added some Milliliters of water in periodic intervals. By this reaction we obtained the acetoacetanilide intermediates **3a-c** in good yields.

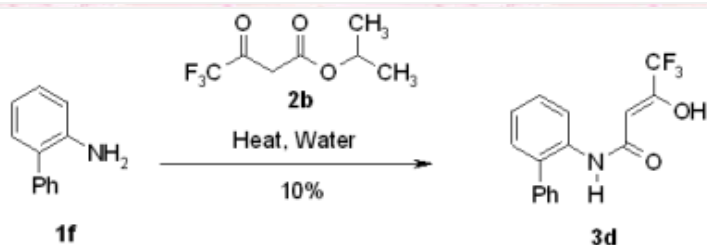


Trifluoroacetoacetate **2b** (R = CF₃) reacted at the same reaction conditions with anilines **1a-c** by addition of water to slightly different anilide isomers. Spectral and analytical data, revealed, that addition of water took place and stable ketone-hydrates were isolated. This seems to be also the main reason, why Schlosser's watering protocol [5] leads to anilide isomers: because of protected keto groups.

When 3-Chloro- or 2,3-dichloroaniline (**1d,e**) was brought to reaction with acetoacetate **2a** in the presence of water, very low yields were obtained from a product, which was assigned by spectral and

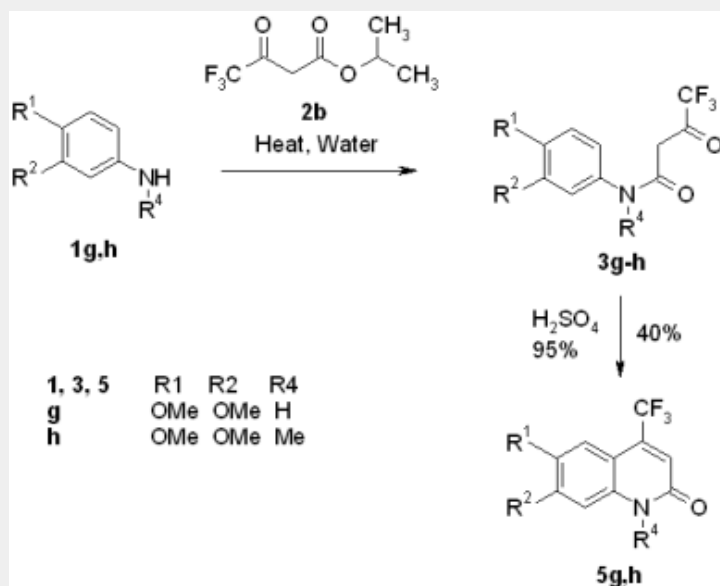


analytical data as the enamine of the reaction product of acetoacetate with 2 molecules of aniline, on both reaction centers, the ester and the keton moiety.



The reaction of 1-phenylaniline **1f**, having a phenyl group as desactivating substituent, with trifluoroacetoacetate **2b** gave in low yields the anilide **3d**, which exists according to spectral data predominantly as the enol tautomer.

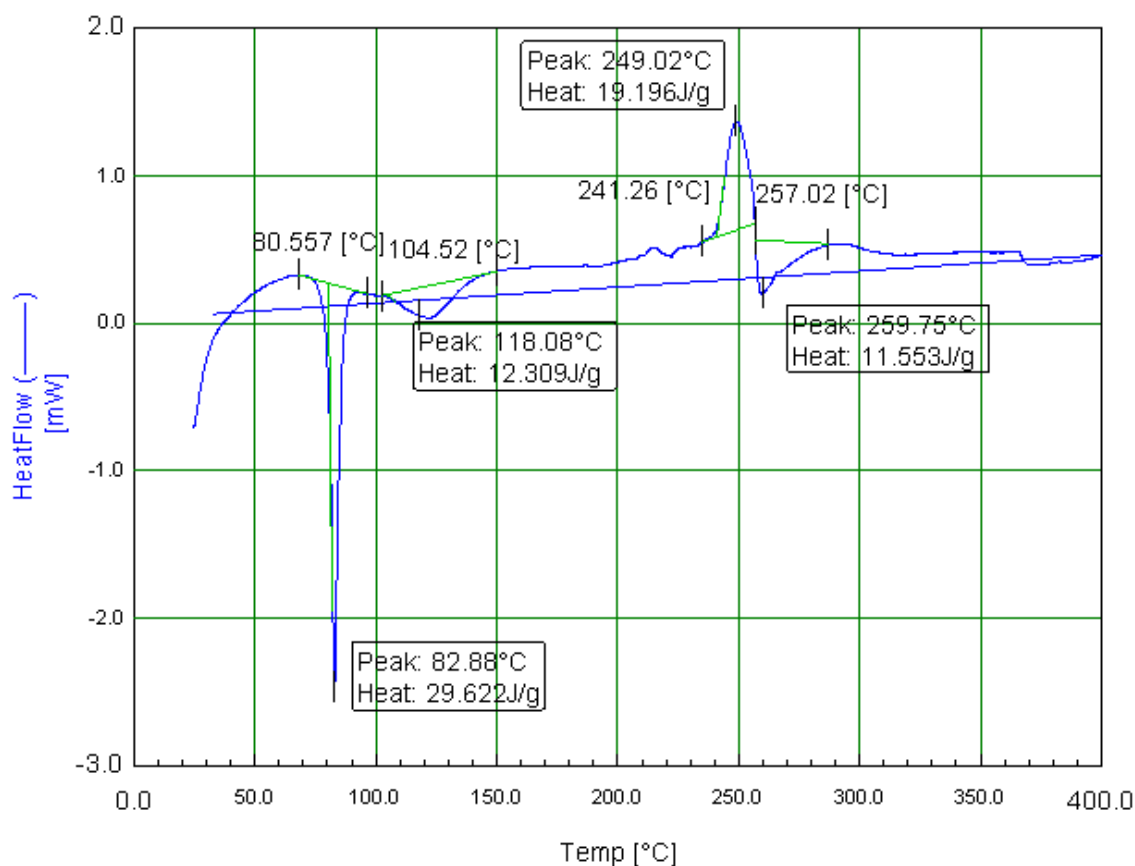
Ringclosure Reactions



Recently we have published the synthesis of 6,7-dimethoxy-4-trifluoromethylquinolones [3,4] in a one pot reaction from anilines **1g, h** by thermal condensation to an about 9:1 mixture of **3** and **4**, which were subsequently cyclized by heating in 75% sulfuric acid. After recrystallization pure, isomer-free 2-quinolones **5g,h** were obtained; the yields were ranging between 85-95%.

Application of the watering method followed by a cyclization in 95% sulfuric acid as described in ref. [5] did neither improve the isomer ratio nor the yields, because after recrystallization only 40% was obtained. Maybe the application of 95% sulfuric acid is not suitable for the methoxy groups.

Attempts to cyclize the deactivated anilides **3** and **7** to corresponding quinolones **5**, using 75% or 95% sulfuric acid, failed, because either no reaction took place, or - at prolonged reaction times - mainly decomposition products were obtained; probably



the influence of chloro-, dichloro- or trifluoromethyl groups prevents the attack at the aromatic aniline ring.

To investigate thermal ringclosure conditions of **3a-c**, thermal behavior was investigated by thermoanalytical methods. Differential thermal scanning calorimetry (DSC) shows that after the melting area (90-105 °C) another endothermic area follows (105-120 °C onset), and at about 210-250 °C an exothermic reaction is visible, in some cases followed by a further melting area at about 250-275 °C.

As an example the DSC diagram for **7a** is shown left.

Attempts to transform these findings to a preparative scale, however, failed and only decomposition products were obtained.

Experimental

General procedure for the preparation of acetanilides **3**, **7** and **8**:

A mixture of one equivalent of acetoacetate or trifluoroacetoacetate was heated to 130 °C for 1-6 hours. During this period every 20 min water (2 mL) was added. Then the mixture was cooled in an ice-bath, triturated with methanol or hexane, the solid filtered and washed with the same solvent. After crystallization from either methanol, hexane or ligroin, colorless or brownish prisms were obtained; the yield was 10-70 % for anilides **3**, 25-40% for anilides **7** and 8% for enamines **8**.

Typical spectroscopical signals:

IR signals for acetoacetanilides **3a-c**: ketone at 1715-1730 cm^{-1} , amide at 1659-1673 cm^{-1} ;

for the enolic structure of acetoacetanilide **3d**: no ketone signal, amide signal at 1670 cm^{-1} ;

for acetanilides **7a-c**: no ketone signal, amide signal at 1644-1673 cm^{-1} ;

for enamines **8**: amide signal at 1650-1660 cm^{-1}

NMR signals for acetoacetanilides **3a-c**: CH_2 group as singlets at 3.63-3.65 ppm, methyl group as singlets at 2.35-2.36 ppm, NH group as singlets at 9.58-9.59 ppm;

for the enolic structure of acetoacetanilide **3d**: CH as singlet at 5.89 ppm; OH as singlet at 10.15 ppm;

for acetanilides **7a-c**: CH_2 group as singlet at 2.85-2.87 ppm, OH signals as singlet at 5.20-5.36 ppm;

for the enamines **8**: methyl signal as singlets at 1.90-2.02 ppm; CH signal as singlets at 4.87-5.86 ppm.

Acknowledgement

This work was supported by a 1-year-scholarship of the [Austrian Academic Exchange Service](#) for N.S.B.

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