SPECIFIC FEATURES OF REACTIONS OF 2-AMINOBENZOTRIFLUORIDE AND ANTHRANILATES WITH ETHYL CYANOACETATE — EXPEDITIOUS ROUTES TO 3-SUBSTITUTED 4-AMINO- AND 4-HYDROXYQUINOLIN-2(1*H*)-ONES

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Abstract: Simple one-pot four-step syntheses of 3-cyano-4-[2-(trifluoromethyl)phenylamino]- (**6**) and 3-(4-oxo-3*H*-quinazolin-2-yl)-4-hydroxy- (**12**) quinolin-2(1*H*)-ones, compounds of biological importance, from commercially available starting materials were reported. The 2-quinolinones **6** and **12** were obtained in moderate yields by three-component reactions of 2 equivalents of 2-aminobenzotrifluoride (**1**, 2-(trifluoromethyl)aniline) or 2 equivalents of anthranilates **7** with ethyl cyanoacetate (**2**).

Keywords: trifluoromethyl group ; amines ; anthranilates ; quinolinones ; quinazolinones

INTRODUCTION

While engaged in different aspects of chemistry (1), physics (2), and biology (3) of compounds comprising coumarin (2-oxo-2*H*-1-benzopyran) backbone, we required to synthesize their structural analogs – different 3-substituted 4-amino/hydroxyquinolin-2(1*H*)-one derivatives.

Scanning the literature on the subject we found that a wide variety of different methods is now at hand for chemists to synthesize 3-substituted 4-hydroxy- (4,5) and 4-amino- (6,7) 2-quinolinones. But the great majority of these methods require a number of steps, namely, preparation of starting materials and/or isolation of intermediate products.

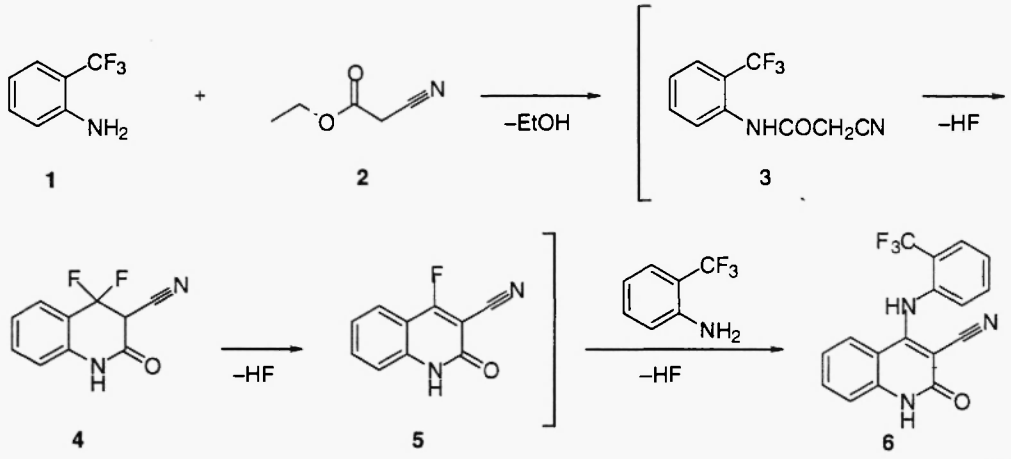
RESULTS AND DISCUSSION

In this communication we wish to report on simple one-pot four-step syntheses of 3-cyano-4-[2-(trifluoromethyl) phenylamino]- (**6**) and 3-(4-oxo-3*H*-quinazolin-2-yl)-4-hydroxy- (**12**) quinolin-2(1*H*)-ones (*cf.* Schemes 1 and 2) from commercially available reagents.

The trifluoromethyl group in 2-aminobenzotrifluoride (**1**) represents an attractive target for its structural modifications and provides an area for developing and testing new strategies and methodologies (8). So Kiselyov and Strekowski reported (9) on heterocyclization reactions of 2-(trifluoromethyl)aniline (**1**) with anions derived from substituted acetonitriles with formation of 3-substituted 2-amino-4-fluoroquinolines. Other reports (10,11) from the same group showed that the treatment of **1** with the lithium enolate of *tert*-butyl acetate furnished a product of acetylation – *N*-[2-(trifluoromethyl)phenyl]acetamide, while anions derived from ethyl cyanoacetate (**2**) and malononitrile were inert (10) toward **1**. The data presented indicate that chemoselectivity of the reaction of ethyl cyanoacetate with **1** thus might constitute the main challenge.

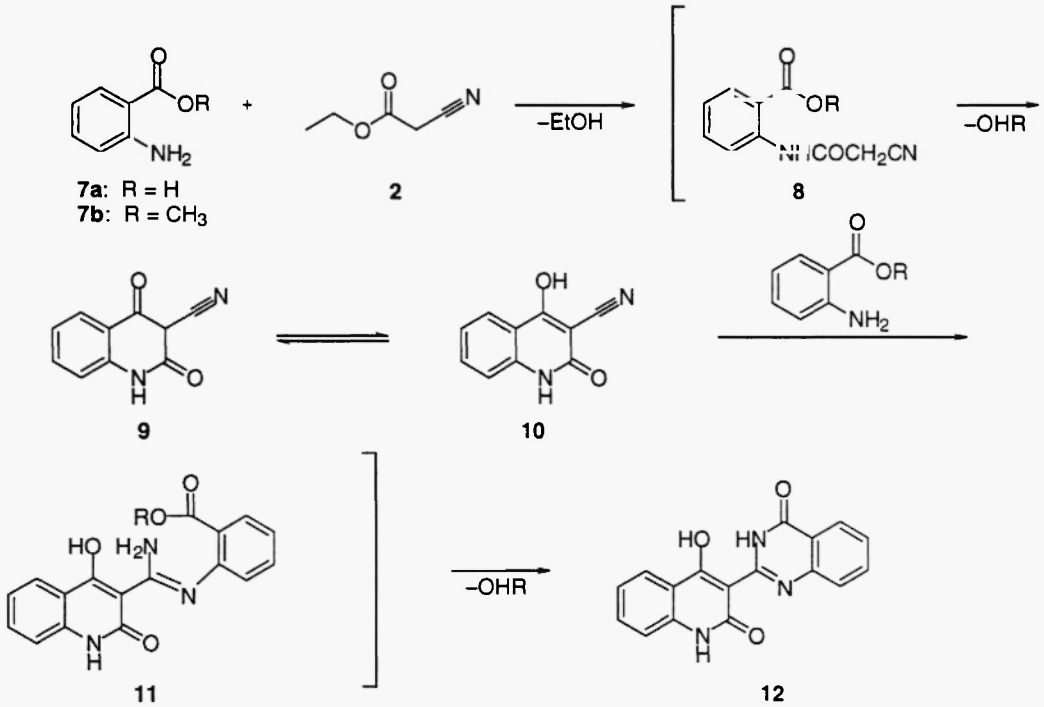
As a result of our studies we found a heterocyclization method to synthesize 4-arylamino-2-quinolinone **6** bearing a trifluoromethyl group on a phenyl fragment. A possible route for a reaction of **1** with **2** is presented in Scheme 1. The formation of compound **6** can be rationalized in terms of a reaction of ethyl cyanoacetate with **1**. In the case

intramolecular cyclization of the resultant adduct **3** with the involvement of the trifluoromethyl function gave **4** and followed by HF-elimination from **4** to afford 4-fluoro-2-quinolinone **5** possessing highly activated position C-4 toward a nucleophilic attack. A spontaneous nucleophilic displacement of the fluorine in **5** by **1** furnished the amino derivative **6**. The structure of **6** was assigned by ^{1}H NMR-, ^{13}C NMR-, ^{19}F NMR- spectral data and IR-analysis ($\nu_{C\equiv N}$ = 2214, $\nu_{C=O}$ = 1639 cm^{-1}).



Scheme 1

Taking into consideration a positive result described in Scheme 1 for the synthesis of 4-aminoquinolone **5**, we continued our studies on condensation reactions of ethyl cyanoacetate with other anilines **7** bearing in *ortho*-position carboxyl functions (Scheme 2). Our purpose was to elaborate a simple method for construction of 4-hydroxyquinolone moiety. As a result we revealed that three-component condensations of 2 molecules of anthranilates **7a**/**7b** with ethyl cyanoacetate took place upon heating with formation of 3-(4-oxo-3*H*-quinazolin-2-yl)-4-hydroxyquinolin-2(1*H*)-one **12**, compound possessing antithyroid activity (12) (Scheme 2). These reactions were carried out without solvents and any other additional reagents and the best yield of **12** (21%) was obtained when anthranilic acid (**7a**) was utilized.



Scheme 2

A probable pathway to compound **12** by the reaction of **7a/7b** with **2** is presented in Scheme 2. The first step is acylation of *ortho*-aminocarbonyls **7a/7b** with ethyl cyanoacetate and formation of Claisen-type condensation precursors 2-[(cyanoacetyl)amino]benzoates (**8**). The primary amide **8** (if R = Me, ref. 5, 12) is known compound, but it was not isolated during the reaction course (13). Further intramolecular Dieckmann condensation of **8** afforded 2,4-dihydroxyquinolines **9** → **10** where 2-quinolinone tautomer **10** is the preferred structure (14). The formation of pyrimidine derivative **12** is assumed (15) to proceed *via* addition of the amino function of **7** to the cyano group in **10** with formation of intermediate amidine **11** which undergoes intramolecular cyclization by nucleophilic attack on the carbonyl function to yield the pyrimidine **12**.

CONCLUSIONS

In summary, the main advantage of the methods suggested above for the synthesis of 3-cyano-4-[2-(trifluoromethyl)phenylamino]- (6) and 3-(4-oxo-3*H*-quinazolin-2-yl)-4-hydroxy- (**12**) quinolin-2(1*H*)-ones, compounds of biological importance, is that intermediate products were not isolated and the title compounds **8** and **12** were formed directly from starting materials. It is also important that these one-pot reactions provided a simple preparation of 2-quinolinone moiety. It is pronounced that these reactions (Schemes 1 and 2) were carried out without any additional reagents. The presented reactions should also be useful additions to the known methods for the preparation of 3-substituted 4-amino- and 4-hydroxyquinolin-2(1*H*)-one derivatives and extension of the scope of the methods is now under investigation.

EXPERIMENTAL

General procedures. Melting points (°C) were measured with a Büchi melting point apparatus and were uncorrected. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). ^{1}H NMR-, ^{13}C NMR-, and ^{19}F NMR- spectra were recorded on Bruker AMX-400 spectrometer in DMSO-d_6 using TMS and $CFCl_3$ as the respective internal standards (chemical shifts in δ ppm). Combustion analyses of all new compounds synthesized gave satisfactory microanalytical data. Infrared spectra (IR) were recorded in KBr pellets on an IBM 486 PC computer-controlled Specord M-80 spectrometer. Glassware was oven-dried and starting materials were commercially available and were purchased from Aldrich.

Preparation of ***3-cyano-4-[2-(trifluoromethyl)phenylamino]-quinolin-2(1H)-one (6)****

A mixture of 2.5 ml (2mmol) of 2-aminobenzotrifluoride (**1**) and 1.06 ml (1mmol) of ethyl cyanoacetate was refluxed with vigorous stirring in a Teflon® flask* for *ca.* 1 hour (the reaction was monitored by TLC). On cooling to room temperature, the reaction mixture was left aside for *ca.* 72 hours. A precipitate formed was filtered, washed with ethanol and then additionally twice recrystallized from ethanol with charcoal to afford 0.64 g (19% yield) of the title compound **6** as colorless crystals with mp 274-5 °C (dec). ^{1}H NMR (400 MHz): δ 7.25-7.31 (m, 2H, Ar*H*); 7.62-7.66 (m, 3H, Ar*H*); 7.76 (ddd, 1H, *J* = 7.4, 7.4, 0.8Hz, Ar*H*); 7.84 (m, 1H, Ar*H*); 8.30 (d, 1H, *J* = 8.1 Hz, Ar*H*); 9.73 (s, 1H, N*H*); 11.55 (s, 1H, CON*H*). ^{13}C NMR (100.6 MHz): δ 80.5; 112.5; 114;9; 116.6 (*C*H); 122.3 (*C*H); 123.5 (*C*H); 123.8 (q, $^1J_{C\text{-}F}$ = 272Hz); 126.9 (q, $^3J_{C\text{-}F}$ = 4Hz,*C*H); 128.6 (q, $^2J_{C\text{-}F}$ = 29Hz); 129.5 (*C*H); 132.2 (*C*H); 133.4 (*C*H); 133.5 (*C*H); 136.4 (q, $^3J_{C\text{-}F}$ ≈ 4Hz); 139.3; 155.6; 161.4. ^{19}F NMR (377.4 MHz): δ –59.6 (s). IR (KBr), cm^{-1}: ν 3416 (NH), 3256 (NH), 3016, 2885, 2214 (C=N), 1639 (C=O), 1600, 1520, 1318. Anal. Calcd. for $C_{17}H_{10}F_3N_3O$ (329.28): C 62.01; H 3.06; N 12.76. Found: C 62.21; H 3.08; N 12.89.

** Caution is to be taken in handling this reaction – strong HF liberation*

Preparation of ***3-(4-oxo-3H-quinazolin-2-yl)-4-hydroxyquinolin-2(1H)-one (12)***

Method ***A****:* A mixture of 1.37 g (1mmol) of anthranilic acid (**7a**) and 1.06 ml (1mmol) of ethyl cyanoacetate was refluxed with stirring for 45-50 min (the reaction was monitored by TLC). After cooling to room temperature the reaction mixture was dissolved in 5 ml of hot DMF. After cooling a precipitate formed was filtered and additionally washed with ethanol/DMF and then ethanol. Subsequent recrystallization from DMF with charcoal afforded 0.32 g (21% yield) of the title compound **12**.

Method ***B****:* A mixture of 2.6 ml (2mmol) of methylanthranilate (**7b**) and 1.06 ml (1mmol) of ethyl cyanoacetate was refluxed with stirring for *ca.* 5-6 hours (the reaction was monitored by TLC). After cooling to room temperature the reaction mixture was dissolved in 5 ml of hot DMF. On cooling a precipitate formed was filtered and additionally washed with ethanol/DMF and then ethanol. Subsequent recrystallization from DMF with charcoal afforded 0.42 g (14% yield) of the compound **12**.

^{1}H NMR-, IR-spectral data, and Mp of the compound **12** have been compared to the data of the authentic sample (12) and are identical.

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