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Tetrahedron Letters 47 (2006) 6365–6368
Tetrahedron Letters

Synthesis of substituted 2-amino-4-quinazolinones via *ortho*-fluorobenzoyl guanidines

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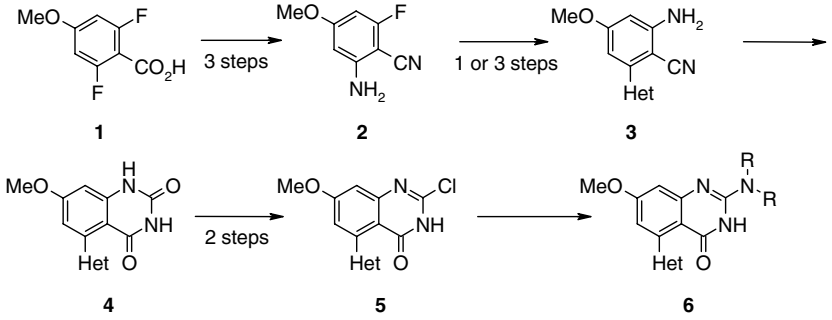
Received 1 June 2006; revised 21 June 2006; accepted 30 June 2006
Available online 24 July 2006

Abstract—A novel route to 12 substituted 2-amino-4-quinazolinones is described. Starting from 2,6-difluoro-4-methoxybenzonitrile, substitution of one of the fluorine atoms either directly or indirectly with heterocycles (e.g., pyridyl, thiazolyl, pyrazolyl) followed by hydrolysis of the nitrile gave a series of *o*-fluorobenzoic acid derivatives. Condensation with a set of six N,N-disubstituted guanidines followed by base-promoted ring closure afforded 2-amino-4-quinazolinone derivatives.

Quinazolinones and quinazolines are fused heterocycles that are of much interest due to their diverse biological activities.[1] During our programme to discover novel α_1 adrenergic antagonists,[2] we prepared substituted 2-chloro-4-quinazolinones **5** as precursors to a series of 2-aminoquinazolinones **6** (Scheme 1). 2,6-Difluoro-4-methoxybenzoic acid **1** was converted into nitrile **2**, followed by the introduction of a heterocyclic substituent (either carbon or nitrogen linked) and conversion of **3** into quinazolinedione **4**. Quinazolinedione **4** was then chlorinated and partially hydrolysed and the amine substituent introduced via the displacement of chlorine in **5**. Unfortunately, when we came to apply this route to examples where Het = 2-pyridyl or 1-(2-methyl)imidazolyl, the chlorination of **4** failed or proceeded in a very low yield, possibly due to the low solubility of the starting material or sensitivity of the product towards aqueous work-up.

This letter describes an alternative route (Scheme 2) that proceeds from substituted *o*-fluorobenzoic acids **7a**–**e**, via acylation and ring closure of intermediate acyl guanidines **8a**–**l**.

The preparation of the 2-pyridyl and 2-thiazolyl substituted benzoic acids **7a**,**b** commenced with



Scheme 1.

Keywords: Quinazolinones; Guanidines; *o*-Fluorobenzoic acids; Acylation; Nucleophilic aromatic substitution.
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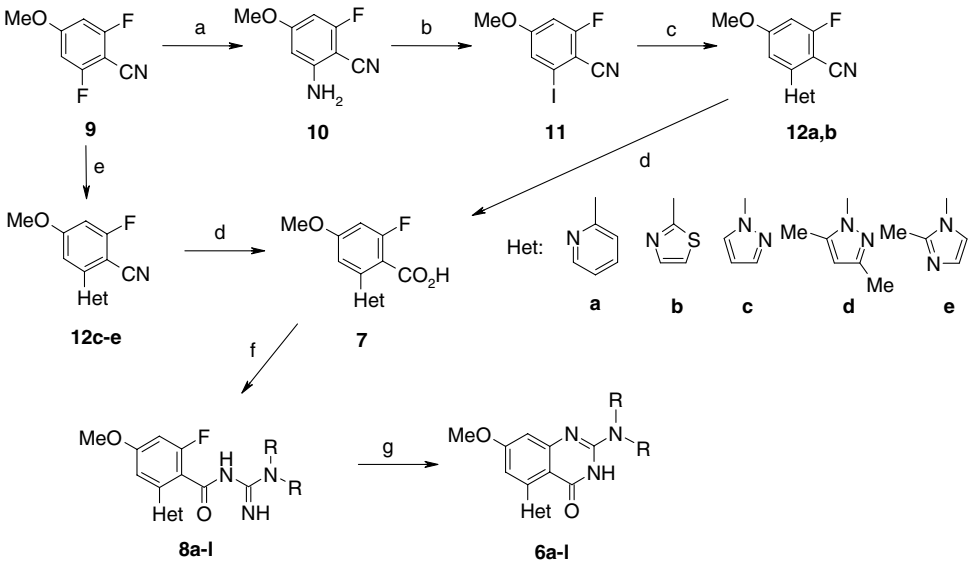
doi:10.1016/j.tetlet.2006.06.168



Scheme 2. Reagents and conditions: (a) $NH_{3(g)}$, DMSO, 90 °C, 16 h, 88%; (b) $NaNO_2$, concd aq HCl, −10 °C, 1 h, then KI, −10 °C to 20 °C, 16 h, 88%; (c) (2-pyridyl)tributylstannane or (2-thiazolyl)trimethylstannane (2 equiv), CuI (20 mol %), LiCl (4 equiv), $Pd(PPh_3)_4$ (10 mol %), dioxane, reflux 90 min, 90–96%; (d) concd HCl, reflux, 2–6 h, 50–93%; (e) Het-H, NaH, NMP, 20 °C, 23–39%; (f) *N*,*N*-carbonyldiimidazole, DMF, 20 °C, 30 min, then **17a**–**f**, Cs_2CO_3, 20 °C, 18 h and (g) $KOBu^t$ (3 equiv), DME, reflux, 1–4 h.

difluorobenzonitrile **9**, which was treated with ammonia in DMSO to give **10**, followed by a Sandmeyer reaction to give **11**.[3] Palladium-catalysed cross-coupling of the iodide **11** with (2-pyridyl)tributylstannane[4] or (2-thiazolyl)trimethylstannane[5] afforded **12a**,**b**. The yields of both reactions were very high, illustrating the value of performing this type of cross-coupling in the presence of catalytic copper(I) iodide and an excess of lithium chloride. Other conditions (e.g., $Pd_2(dba)_3$, Ph_3As, CuI, DMF)[6] or using 2-thiazolylzinc bromide gave inferior yields. Hydrolysis of **12** under forcing conditions (concd HCl, reflux) gave the required acids **7a**,**b**. We also attempted to prepare three N-linked heterocyclic derivatives **7c**–**e**: two N-linked 1-pyrazolyl derivatives **7c**,**d** and N-linked 2-methylimidazolyl derivative **7e** (Scheme 2) via displacement of one of the fluoro groups in **9** by the anion of the relevant heterocycle. This first step was successful in each case, but the desired products **12c**–**e** were formed only in modest yields (23–39%), accompanied by products arising from substitution of both fluorines. Nitriles **12c** and **12d** were then hydrolysed, as before, in high yield to give **7c**,**d**. To our surprise, the related 2-methyl-1-imidazolyl analogue **12e** was inert to acidic hydrolysis (no reaction, 16 h). We did not attempt hydrolysis under basic conditions as we anticipated that the nucleophilic substitution of the fluorine would be more rapid.

We wondered whether **12e** was unusually hindered (yet the successful hydrolysis of the dimethylpyrazolyl analogue **12d** would suggest otherwise), or whether the basicity of the imidazole ring might have been responsible (but the pyridyl analogue **12a** would have a similar basicity). As a control experiment we attempted to hydrolyse **11** under the same conditions and again observed no reaction, even after 4 days at reflux. We therefore deduce that the common structural feature in all the analogues that underwent successful hydrolysis was an sp^2 nitrogen atom adjacent to the nitrile that can assist hydrolysis (Fig. 1). Neighbouring group participation by the heterocycle via hydrogen bonding to water or an ion pair with chloride are possible alternative reaction pathways for the hydrolysis of both the nitrile and amide. Compounds **12e** and **11** cannot help present the nucleophile in this way, and are therefore unreactive.

Therefore, to prepare **7e** we converted **1** into its *tert*-butyl ester **13**[7] (Scheme 3), which when reacted with 2-methylimidazole gave **14**. Cleavage of the *t*-butyl ester **14** (presumably through a S_N1 or E1 mechanism)[8] proceeded without difficulty.

The syntheses of the requisite guanidine derivatives **17a**–**f** and the target quinazolinones **6a**–**l** are shown in Schemes 4 and 2, respectively. Thus, a set of six N,N-disubstituted amines **15a**–**f**[9] was treated with *N*,*N*′-bis-(Boc)-*S*-methylisothiourea in the presence of mercuric chloride[10] to give **16a**–**f**, followed by acidic deprotection to give **17a**–**f**, as their trifluoroacetate salts.

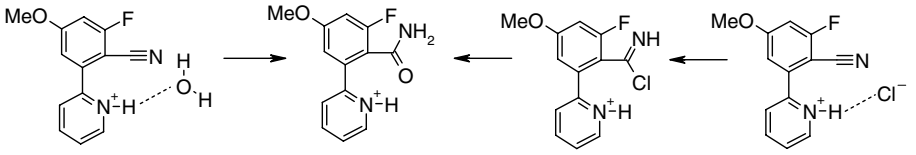
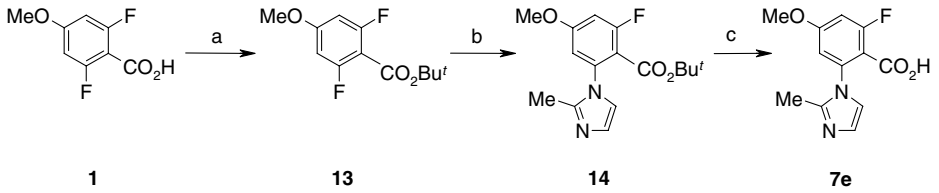
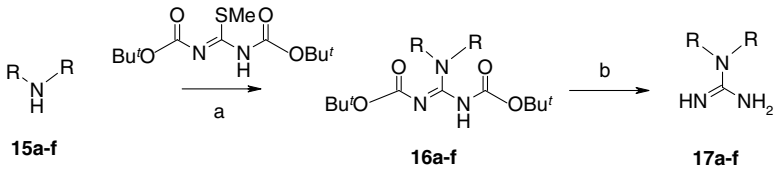


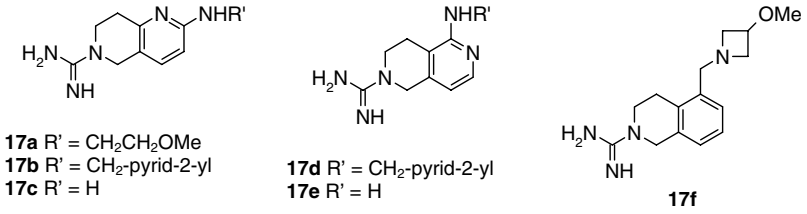
Figure 1.



Scheme 3. Reagents and conditions: (a) $Me_2NCH(OBu^t)_2$ (4 equiv), toluene, 80 °C, 2 h, 92%; (b) 2-methylimidazole, NaH, NMP, 100 °C, 20 h, 41%; (c) TFA/CH_2Cl_2, 20 °C, 4 h, 84%.



Scheme 4. Reagents and conditions: (a) $HgCl_2$, Et_3N, CH_2Cl_2, 20 °C; (b) 50% TFA/CH_2Cl_2 or $HCl_{(g)}$, 20 °C.



Acids **7a**–**e** were activated using *N*,*N*′-carbonyldiimidazole in DMF and allowed to react with the guanidines in the presence of caesium carbonate to form **8a**–**l**, the added base acting to neutralise the trifluoroacetic acid of the salts. Ring closure of acylguanidines **8a**–**l** was accomplished using potassium *t*-butoxide in 1,2-dimethoxyethane at reflux. The products made and the yields are shown in Table 1.

From Table 1 it can be seen that formation of the acyl guanidines proceeded in good to excellent yields. However, the yields for the cyclisation step were highly variable and often low. Smith and co-workers[11] reported the reaction between various *ortho*-fluorobenzoyl chlorides and a series of 2-aminoheterocycles, such as 2-aminopyrimidine. They observed mostly formation of the acyl guanidine, but hetero-fused quinazolinones were also isolated in low to moderate yields. As we needed to obtain analytically pure samples for biological screening as rapidly as possible, we did not examine many reaction conditions for this step and the yields usually refer to a single attempt on 0.5 mmol scale. It is evident that there is a considerable scope for improving this methodology. If this method of preparing quinazolinones **6** is compared with the one we recently reported,[1] it is evident that using acyl guanidine intermediates leads to a somewhat shorter synthesis, though with low yields associated with trying to achieve selective nucleophilic substitution of difluorobenzonitrile **9**, and ring closure of acyl guanidines **18**. Nevertheless, we successfully prepared four target compounds (**6a**, **d**, **e** and **j**) that eluded us by the other route.

Table 1.

Guanidine **17**	Carboxylic Acid **7**	Acylguanidine (Yield) (%)	Quinazolinone[a] (Yield) (%)
a	**a**	**8a** (45)	**6a** (75)
a	**b**	**8b**[b]	**6b** (23)
a	**d**	**8c** (91)	**6c** (44)
a	**e**	**8d** (50)	**6d** (17)
b	**a**	**8e**[b]	**6e** (20)
c	**b**	**8f**[b]	**6f** (27)
c	**c**	**8g** (64)	**6g** (15)
c	**d**	**8h** (95)	**6h** (65)
d	**c**	**8i** (92)	**6i** (8)
d	**e**	**8j** (95)	**6j** (30)
e	**c**	**8k** (98)	**6k** (38)
f	**c**	**8l** (98)	**6l** (37)

[a] Yields are unoptimised and refer to analytically pure material, usually from a single attempted reaction.
[b] Crude product used directly in cyclisation.

In summary, we have reported a new method for the synthesis of 5-heterocycle-substituted quinazolin-4-ones from a series of *ortho*-fluorobenzoic acids and N,N-disubstituted guanidines. In addition, we found that the ease of acidic hydrolysis of certain 2-heterocycle-substituted benzonitriles was strongly dependent on the nature of the heterocycle, implying that hydrolysis was aided by the presence of an sp^2 nitrogen atom on the heterocycle. In one case where such an atom was not present and the nitrile resisted hydrolysis, an alternative route via the *t*-butyl ester was developed. A total

of twelve quinazolinones were prepared and screened for the activity as α_1 adrenergic antagonists; the results will be reported elsewhere.

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