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SYNTHESIS OF 5-HETEROCYCLIC SUBSTITUTED QUINAZOLIN-4-ONES *VIA* 2-AMINOBENZONITRILE DERIVATIVES

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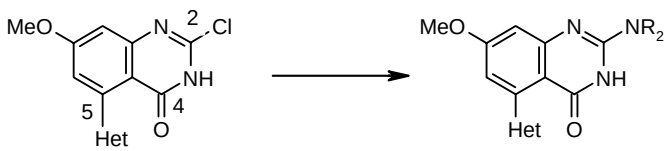
Abstract – Two routes to prepare a series of six 5-heterocyclic substituted 2-chloro-7-methoxyquinazolin-4-ones are described, where the heterocycle is a substituted or unsubstituted 1-pyrazolyl, 5-pyrazolyl or 2-thiazolyl group. Both routes proceeded *via* key 2-aminobenzonitrile intermediates.

To mark the 65th birthday of Professor Barry Trost, from whom I learned so much.

INTRODUCTION

In connection with a programme to discover novel, selective α_1-adrenergic antagonists, we wished to prepare a series of 5-heterocyclic substituted quinazolin-4-ones (**9a-f**) as intermediates, as shown below.



9a-f **target α-antagonists**

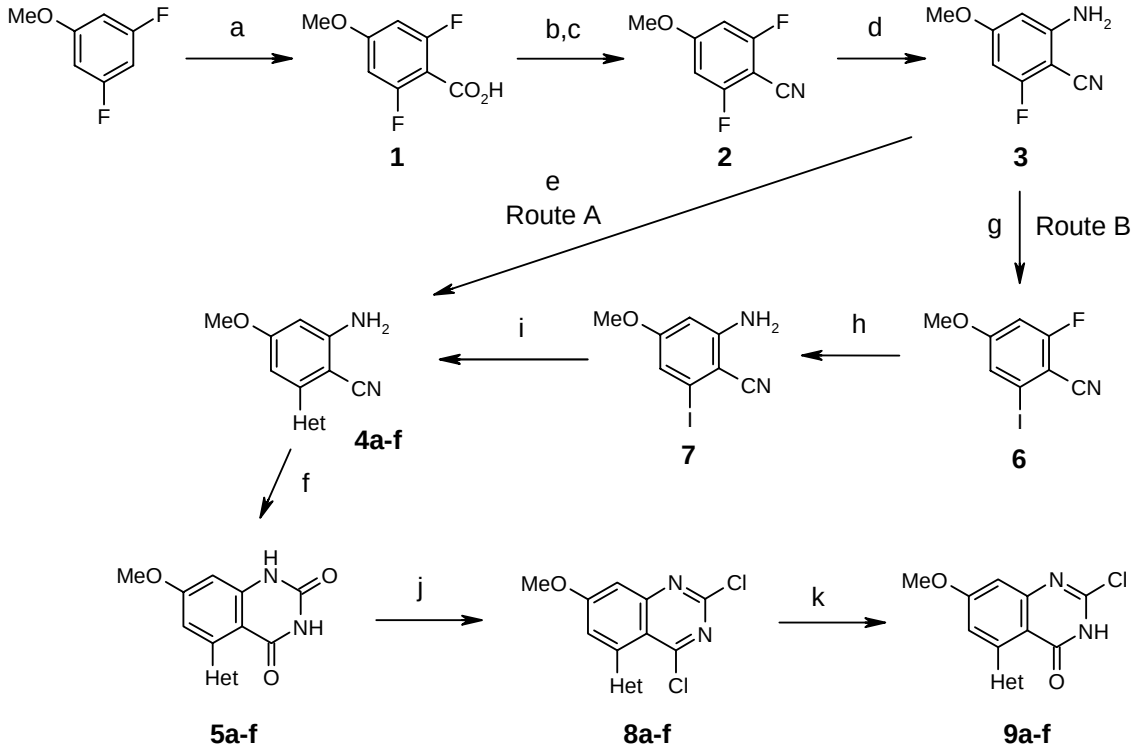
This paper describes two similar routes where the heterocycle is a substituted or unsubstituted 1-pyrazolyl,

5-pyrazolyl or 2-thiazolyl group, and a 2-aminobenzonitrile functions as a key precursor to the quinazoline ring system. We also attempted the synthesis of other heterocyclic-substituted analogues, but these routes were unsuitable and alternatives had to be developed; they will be described elsewhere.

RESULTS AND DISCUSSION

The synthetic routes are shown in Scheme 1. The plan was to prepare difluorobenzonitrile analogue (**2**), and replace both fluorines in turn with a heterocycle (either nitrogen or carbon linked) and an amino group, leading to compounds (**4a-f**).

Scheme 1



Reagents and conditions: a: n-BuLi, THF, −78°C, then $CO_{2(s)}$, 86%; b: $(COCl)_2$, CH_2Cl_2, 20°C, then $NH_{3(aq.)}$, THF, 71%; c: $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 0-20°C, 87%; d: $NH_{3(g)}$, DMSO, 90°C, 16 h, 88%; e: Het-H (1.3 eq.), NaH, NMP, 80°C, 16 h; f: CO_2 (40 bar), DBU (3 eq.), DMF, 120°C, 18 h; g: $NaNO_2$, conc. aq. HCl, −10°C, 1 h, then KI, −10°C to 20°C, 16 h, 88%; h: $NH_{3(g)}$, DMSO, 120°C, 16 h, 92%; i: either 1-methyl-5-tributylstannyl-1*H*-pyrazole, 5 mol% Pd_2(dibenzylideneacetone)$_3$, tri(2-furyl)phosphine, dioxane, reflux 2 h, 47% or 1-ethoxymethyl-1*H*-pyrazole, n-BuLi, THF, then $ZnCl_2$, then 5 mol% Pd_2(dibenzylideneacetone)$_3$, tri(2-furyl)phosphine, THF, reflux 20 h, 47% or 2-thiazolylzinc bromide, 5 mol% Pd_2(dibenzylideneacetone)$_3$, tri(2-furyl)phosphine, THF, reflux 20 h, 57%; j: $POCl_3$ (25 eq.), i-Pr_2NEt (2.4 eq.), reflux, 3 h; k: 2M aq. NaOH (5 eq.), dioxane, 20°C, 2 h.

Previous work from these laboratories[1] had shown that 2-aminobenzonitrile derivatives similar to **4** were readily converted into 4-amino-2-quinazolinones, and thence onto 4-amino-2-chloroquinazolines. Whilst the 4-amino group of these latter compounds could be exchanged for a hydroxyl, the synthesis was lengthy

and cumbersome to perform. Mizuno, however, has demonstrated the direct conversion of 2-aminobenzonitriles into quinazoline-2,4-diones.[2] We have adapted his conditions for the current work, which is described here.

Therefore, following the work of Gray *et. al.*,[3] 3,5-difluoroanisole was deprotonated cleanly between the two fluorine atoms, using n-butyllithium in THF at -78°C. Solid carbon dioxide pellets were added, and the mixture allowed to warm to room temperature to give, after work-up, the acid (**1**), in good yield. Compound (**1**) was then converted into nitrile (**2**), *via* the primary amide, using standard conditions.[4] Trial reactions of **2** with deprotonated hetcyclesero, e.g. pyrazole, were complicated by the displacement of both fluorine atoms, even under mild conditions, leading to a mixture of products. Consequently, we decided to introduce the amino group first, using the conditions described by Hynes.[5] Thus, heating **2** with a solution of ammonia in DMSO at 90°C led to a high yield of **3**, though it was necessary to re-saturate the solution with ammonia twice to ensure complete conversion. Presumably, introduction of the amino group deactivates the aromatic ring sufficiently that the second substitution is significantly slower and so only the product of mono-substitution is formed.

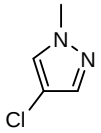
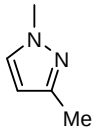
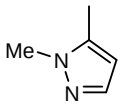
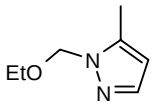
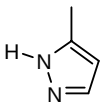
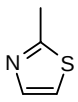
With compound (**3**) in hand, we investigated ways to introduce the heterocycles. For the nitrogen-linked heterocycles (Route A), simply heating **3** with the deprotonated heterocycle (NaH, NMP) at 80°C overnight resulted in displacement of the fluorine atom to give **4a-c**. The yields with pyrazole, 4-chloropyrazole and 3-methylpyrazole were 83%, 45%, and 47%, respectively.

Initial attempts to use Mizuno's conditions[2] (20°C, 1 bar carbon dioxide, DBU, DMF) to transform **4a** into the quinazolinedione (**5a**) were unsuccessful due to lack of reaction. However, we discovered that by using more forcing conditions (120°C, 40 bar carbon dioxide) gave the desired product after acidic workup. The reaction was readily set up using a stainless steel autoclave vessel fitted with a pressure gauge and release valve. The aminonitrile, DBU and DMF were mixed and the solution cooled in a isopropanol/carbon dioxide bath. Pellets of solid carbon dioxide were then added carefully and the vessel sealed. The vessel was then heated slowly to 120°C in an oil bath, and the internal pressure was adjusted to 40 bar using the release valve, as necessary. Excellent yields were obtained for all the *N*-pyrazolyl analogues (**5a-c**); these, and the yields for later intermediates (**5d-f**, **8a-f** and **9a-f**) are shown in Table 1.

Next, we turned our attention to some carbon-linked heterocyclic analogues (**4d-f**), which we envisaged making *via* cross-coupling reactions between the iodo compound (**7**) and metallated heterocycles (Route

B). Compound (**3**) was converted into **6** using a standard Sandmeyer reaction,[5] and reaction with gaseous ammonia under slightly more forcing conditions than for compound (**2**), afforded **7**.

Table 1: Yields of products

Het	Compound Number (yield)		
	**5a** (75%)	**8a** (88%)	**9a** (78%)
	**5b** (95%)	**8b** (58%)	**9b** (91%)
	**5c** (98%)	**8c** (76%)	**9c** (87%)
	**5d** (93%)	**8d** (95%)	**9d** (61%)
	**5e** (60%)	-	-
	-	**8e** (78%)	**9e** (40%)
	**5f** (59%)	**8f** (71%)	**9f** (82%)

The tributylstannane derived from 1-methylpyrazole[6] was coupled to **7** using palladium trifurylphosphine as catalyst in dioxane at reflux. As a precursor to the 5-pyrazolyl analogue without a nitrogen substituent, we decided to cross couple **7** with 1-ethoxymethyl-1*H*-pyrazol-5-ylzinc chloride,[7] generated *in situ*, again using palladium trifurylphosphine as catalyst. The thiazolyl group was introduced using commercially

available 2-thiazolylzinc bromide[8] in THF under conditions analogous to **4e**. Compounds (**4d-f**) were then cyclised to quinazolinediones (**5d-f**), under the same conditions as above.

We encountered some difficulties in achieving chlorination of the quinazolinediones (**5a-f**). This transformation is usually achieved using phosphorous oxychloride and *N*,*N*-diethylaniline at reflux.[9] Under these conditions, or a number of alternatives, e.g. $POCl_3$,[10] $POCl_3$/dimethylaniline, tetraethylammonium chloride/MeCN/reflux,[11] phenylphosphonic dichloride at 150°C,[10] thionyl chloride/mesyl chloride, reflux, we either recovered a significant amount of starting material, or undesired products. We deduced that the very low solubility of the quinazolinediones might be responsible, so, as these heterocycles are acidic (pKa = 9.6),[12] the addition of a strong base, such as Hünig's base,[13] was thought to be beneficial. This was indeed the case, and led to smooth conversion to product in 3 to 16 h. Care had to be taken during quenching the reaction to avoid adventitious hydrolysis back to starting material.

For convenience, the ethoxymethyl protecting group of **5e** was cleaved (2N HCl, EtOH, reflux, 7 h) before performing the chlorination step (to give **8e**). Finally, selective hydrolysis of dichloroquinazolines (**8a-f**) using sodium hydroxide in aqueous dioxane gave the desired quinazolinones (**9a-f**).

In summary, we have described two routes to a set of six novel quinazolinone derivatives that bear nitrogen- or carbon-linked heterocycles at the 5 position.

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