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2-Chloroquinazoline. Synthesis and reactivity of a versatile heterocyclic building block

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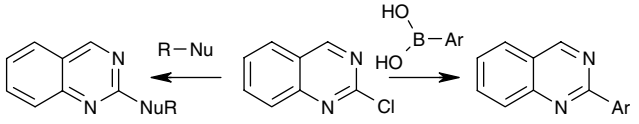
Abstract—Starting from 2,4-dichloroquinazoline, various methods for the selective removal of the 4-chloro substituent were tested, including catalytic hydrogenation, metal–halogen exchange, metal hydride reduction and reduction with tributyltin hydride—the latter both in a radical and in a Stille-type reaction. Amongst these, the most efficient method was found to be the Stille-type coupling. Furthermore, we have studied the reactivity of 2-chloroquinazoline and found it to act as a versatile building block for the direct introduction of the 2-quinazolinyl moiety.

1. Introduction

Quinazolines are components of many bioactive compounds and their chemistry has therefore been studied extensively.[1] We wished to introduce a 2-quinazolinyl group into a small focused library to be tested for ion channel modulating activities.

The formation of 2-substituted quinazolines has previously been achieved from aryl amidines, either via cyclisation of an activated 1-aryl-1,3-diazabutadiene derivative[2] or via condensation with 4-cyano- or 4-nitro-activated *o*-fluorobenzaldehydes.[3] This latter method is, however, restricted to benzaldehydes with strong electron-withdrawing substituents. Aldehydes have also been reacted with 2-aminobenzylamine to give 1,2,3,4-tetrahydroquinazolines, which were subsequently oxidised to the corresponding 2-substituted quinazolines.[4] Cross-coupling between phenyl iodide and 3,4-dihydroquinazoline followed by dehydrogenation was reported to give 2-phenylquinazoline.[5]

However, since a general method for the direct incorporation of the 2-quinazolinyl moiety had not been described, we set out to develop a short and effective procedure. 2-Chloroquinazoline **1** was selected as the target intermediate, as we expected it to readily attach to various scaffolds through nucleophilic substitution or palladium-catalysed cross-couplings (Scheme 1).



1

Scheme 1.

The synthesis of 4-chloroquinazoline, and its usefulness for introducing a 4-quinazolinyl moiety, has been described previously,[6,7] but no simple route to **1** was available.[†] A suitable starting point was 2,4-dichloroquinazoline **2**, since it is known to react regioselectively at the 4-position in a variety of reactions,[8] and can be readily obtained from the commercially available 2,4-(1*H*,3*H*)-quinazolinedione (benzoyleneurea). We wished to utilise the difference in reactivity between the two chlorines of **2** in order to reduce selectively the 4-chloro substituent to afford the desired compound **1**.

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[†] Following the execution of most of the experiments described herein, Kanuma et al. described the synthesis of 2-chloroquinazoline in a 70% yield by the reaction of 2,4-dichloroquinazoline with zinc in aqueous ammonia.[8]

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2,4-Dichloroquinazoline **2** was obtained by the treatment of 2,4-(1*H*,3*H*)-quinazolinedione with phosphorous oxychloride according to literature procedures.[9–12] We subsequently examined a number of methods for the selective removal of the 4-chloro substituent (Table 1).

The reason for including an unconventional procedure such as the Stille-type coupling (Table 1 entry 6) was that tributyltin hydride has been reported to reduce acid chlorides to aldehydes in a palladium-catalysed cross-coupling reaction,[13] and in **2** we expected the reactivity of the 4-chloro substituent to be very similar to that of an acid chloride.

In the first approach, using Stille-type conditions, we generated palladium(0) from palladium(II) acetate and tributylphosphine. However, this procedure gave rise to two major by-products, **3** and **4** (observed by LC–MS), and **1** was obtained in only a 35% yield (Scheme 2).

Initially, the formation of **3** was ascribed either to the presence of residual water in the reaction mixture or to a radical mediated reaction with molecular oxygen. Nevertheless, **3** was formed even under strictly anhydrous conditions, and addition of the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol had no effect on the formation of this by-product. Our hypothesis is that reaction of **2** with acetate (from palladium(II) acetate) affords the unstable ester **5**, which hydrolyses the to give **3** during work-up or when analysed by LC–MS (Scheme 3). This is supported by the formation of **3** upon treatment of **2** with potassium acetate in tetrahydrofuran. Likewise, the phosphonium salt **4** was formed by treating **2** with tributylphosphine.

In a second approach, $(PPh_3)_4Pd$ was used as the catalyst, in order to avoid the formation of by-product **5** and accordingly **3**. However, in this case no reaction occurred and only starting materials were observed.

Finally, the treatment of **2** with $(PPh_3)_2PdCl_2$ and tributylphosphine successfully gave **1** in a 52% isolated yield. The side reaction with tributylphosphine was suppressed by formation of the complex between palladium and tributylphosphine prior to the addition of **2**.

The instability of **5** indicated that it might be sufficiently reactive to undergo reduction by catalytic hydrogenation, and whereas the hydrogenation of **2** with Raney nickel as the catalyst had been unsuccessful (Table 1), **5** was indeed reactive enough to afford **1** in a 15% yield (observed by LC–MS) under these conditions. Unfortunately, 63% of by-product **3** was formed as well, so the Stille-type coupling remained the most effective way of converting **2** into **1**.

In order to study the versatility of **1** as a building block we carried out a series of reactions of **1** with thiol and amine nucleophiles as well as with aryl boronic acids (Table 2).

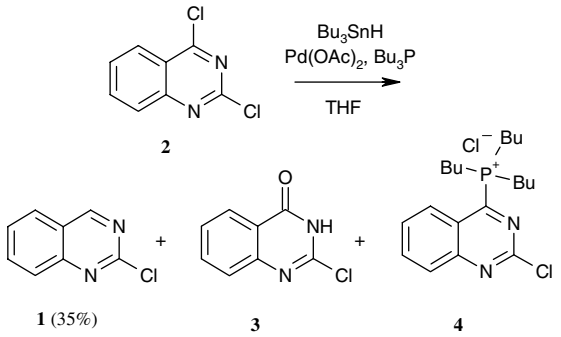
We have found palladium-catalysed Stille-type coupling with tributyltin hydride to be a highly selective way of removing the activated 4-chlorine substituent in 2,4-dichloroquinazoline **2**. Tributyltin hydride is a well-known hydrogen radical donor but this study confirms[13] that, in the presence of a palladium catalyst, tributyltin hydride can also act as a hydride donor. The reaction is mild and could therefore be a suitable method for similar substrates containing either acid-, base- or moisture-sensitive functionalities.

Table 1. Different approaches for the conversion of 2,4-dichloroquinazoline **2** into 2-chloroquinazoline **1**

Entry	Method	Yield of **1** (%)
1	Catalytic hydrogenation	0
2	Metal halogen exchange	0
3	Radical reaction	0
4	Metal hydride reduction	0[a]
5	Clemmensen-type reduction	0[a]
6	Stille-type coupling	52
7	Formic acid reduction	0

Entry 1: Method A: H_2, Pd/C, MeOH, rt. Method B: H_2, Raney Ni, MeOH, rt. Entry 2: Method A: *n*-BuLi, THF, −78 °C. Method B: EtMgBr, diethyl ether, 0 °C. Method C: LDA, THF, −78 °C. Entry 3: Bu_3SnH, AIBN, *tert*-butylmethyl ether. Entry 4: $NaBH_4$, DMF, 50 °C. Entry 5: Zinc powder, AcOH, THF, 70 °C. Entry 6: Bu_3SnH, $(PPh_3)_2PdCl_2$, Bu_3P. Entry 7: HCO_2H, Et_3N, Bu_3P, $Pd(OAc)_2$, dioxane, rt.

[a] The reaction was unselective and only trace amounts of **1** were observed in the reaction mixture, along with a substantial amount of dihydro-2-chloroquinazoline.

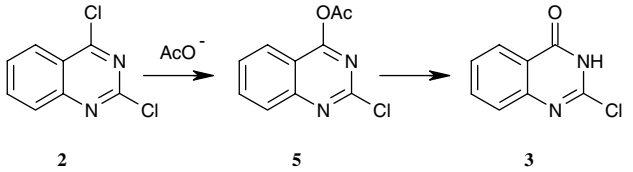


Scheme 2.

2. Experimental

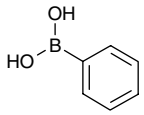
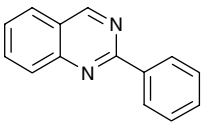
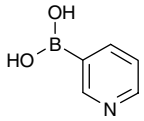
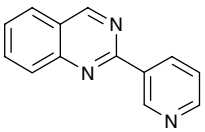
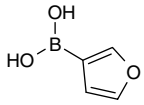
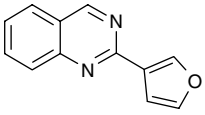
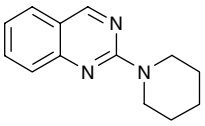
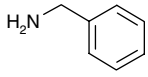
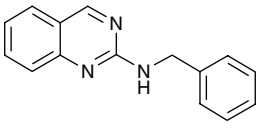
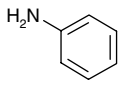
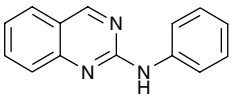
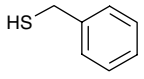
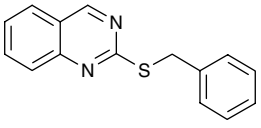
2.1. 2-Chloroquinazoline 1

In a typical experiment, THF was dried through a column of basic aluminium oxide and two solutions were



Scheme 3.

Table 2. Reaction of 2-chloroquinazoline **1** with boronic acids and various nucleophiles

Entry	Reagent		Product		Yield[a] (%)
1		**6a**		**6b**	79
2		**7a**		**7b**	48
3		**8a**		**8b**	63
4		**9a**		**9b**	99
5		**10a**		**10b**	50
6		**11a**		**11b**	55
7		**12a**		**12b**	83

[a] Isolated yields, no optimisation.

made: (I) 200 mg of 2,4-dichloroquinazoline **2** (1.0 mmol) was dissolved in 1.5 ml dry THF under a nitrogen atmosphere. (II) 35 mg of $(PPh_3)_2PdCl_2$ (0.05 mmol) was suspended in 1.5 ml dry THF under a nitrogen atmosphere, and 0.05 ml of Bu_3P (0.2 mmol) was added. Solution II was stirred for 10 min before it was added to solution I. Thereafter, 0.3 ml of Bu_3SnH (1.1 mmol) was added, resulting in a dark coloured reaction mixture. After stirring for 5 h at rt, the reaction mixture was evaporated to dryness and purified by column chromatography, affording **1** in a 52% yield (85 mg).

2.2. General procedure for the reaction of 2-chloroquinazoline 1 with aryl boronic acids. Synthesis of 6b, 7b and 8b

A mixture of **1** (0.61 mmol), the appropriate boronic acid **6a**, **7a** or **8a** (0.90 mmol), K_2CO_3 (3.2 mmol) and $(PPh_3)_2PdCl_2$ (0.033 mmol) in 5 ml solvent (DME/water/EtOH 7:3:2) was placed in a sealed vial and heated to 120 °C for 10 min (**6a** and **7b**) or 15 min (**8b**) using microwave irradiation.[14] The reaction mixture was diluted with water, extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by preparative LC–MS, affording products **6b** (100 mg, 79%), **7b** (60 mg, 48%) or **8b** (75 mg, 63%).

2.3. General procedure for the reaction of 2-chloroquinazoline 1 with benzylthiol and amines. Synthesis of 9b, 10b, 11b and 12b

A mixture of 2-chloroquinazoline **1** (0.50 mmol), the appropriate nucleophile **9a**, **10a**, **11a** or **12a** (0.60 mmol) and K_2CO_3 (0.75 mmol) in 4 ml CH_3CN was placed in a sealed vial. The mixture was heated using MW irradiation. Reaction conditions: **9b**: 50 °C, 20 min; **10b**: 170 °C, 50 min; **11b**: 120 °C, 15 min; **12b**: 120 °C, 30 min. The reaction mixture was diluted with water, extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by preparative LC–MS affording products **9b** (116 mg, 99%), **10b** (50 mg, 50%) **11b** (48 mg, 55%) or **12b** (99 mg, 83%).

Supplementary data

Obtained melting points, MS (ES) and ^1H NMR data as well as results of elemental analyses are included for

compounds **1**, **2** and **6**–**12b**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.121.

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