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Solvent selection in synthesis of 4-(1-arylfluoroethoxy)quinazolines and thienopyrimidines

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ABSTRACT

The nucleophilic aromatic substitution of 4-chloroquinazoline and 6-bromo-4-chlorothieno[2,3-*d*]pyrimidine with 1-aryl-2-fluoroethanols as nucleophilies has been studied focusing on the use of carbonate bases in combination of environmental acceptable solvents. The conversion rate depended on the solvent properties, the acidity of the nucleophile and the nature of the base. By using acetonitrile as reaction medium and K_2CO_3 as base, 2,2,2-trifluoro-, 2,2-difluoro-, and 2-fluoro-1-phenylethanol could efficiently be coupled to 4-chloropyrimidines. Alternatively, employing Cs_2CO_3, allowed for shorter reaction time for these substrates, and also couplings of the non-fluorinated alcohols proceeded well. *tert*-Butanol was also found to be a suitable reaction medium in transformation of the fluoro alcohols. Testing of hydrolytic stability of the 4-alkoxypyrimidines revealed that the fluorinated and non-fluorinated derivatives were labile under acidic conditions, whereas in basic media the fluoroalkoxy derivatives were more stable than their non-fluorinated counterparts.

1. Introduction

Fluorinated molecules are important for the pharmaceutical industry [1–3], but since the chemistry towards these molecules is often hampered by difficult and hazardous process steps, fluorinated pharmaceuticals could be argued not to comply with the principals of sustainable chemistry. However, the improvement in properties of the end product such as bioactivity, bioavailability and metabolic stability, allowing for lower dosing of the drug, might compensate for the lack of sustainability in the fluorination step. Moreover, if the chemistry undertaken with fluorinated precursor molecules can benefit from the electron withdrawing properties of the fluoro atoms, the overall environmental impact of the process could be reduced.

While very little has been reported on aromatic ether formation using 2-fluoro- and 2,2-difluoro-1-arylethanols [4], the patent literature have documented the use of 2,2,2-trifluoro-1-arylethanol in such reactions. Strategies used include converting the alcohol to a good leaving group such as triflate and reaction with a phenol (Williams type) [5], Mitsunobu conditions [6,7], and the coupling of aliphatic alcohols with aryl chlorides or fluorides in the presence of a suitable base [8,9] (Scheme 1). Transition metal catalysed ether formation [10], and microwave assisted reactions [11,12], can also be envisioned. Various challenges can be encountered with these methods such as partial racemisation [13–15], handling of hazardous chemicals, waste issues, the use of strong and flammable bases, or the risk of contaminating the end product with transition metals [16].

Herein, we have investigated the coupling of 1-aryl-2-fluoroethanols in nucleophilic aromatic substitution reactions with 4-chloroquinazoline and 6-bromo-4-chlorothieno[2,3-*d*]pyrimidine [17], a potential building block for kinase inhibitors [18,19]. As the acidity of the alcohol function increase upon fluorination [20,21], we envisioned that more sustainable reaction conditions than those mentioned above could be employed, and wish to communicate our findings.

2. Result and discussion

2.1. Investigation of the coupling chemistry

Quinazoline is an important scaffold in medicinal chemistry [22,23], and 4-chloroquinazoline (**1**) was therefore selected as a model substrate. Compound **1** reacted smoothly with 1-phenylethanol (**2a**) and 2,2,2-trifluoro-1-phenylethanol (**2d**) as nucleophile with sodium hydride as base giving the corresponding 4-alkoxy quinazolines in good yield. However, we were interested in identifying more safe and environmental sound processes, using carbonate bases in combination with a suitable reaction solvent.

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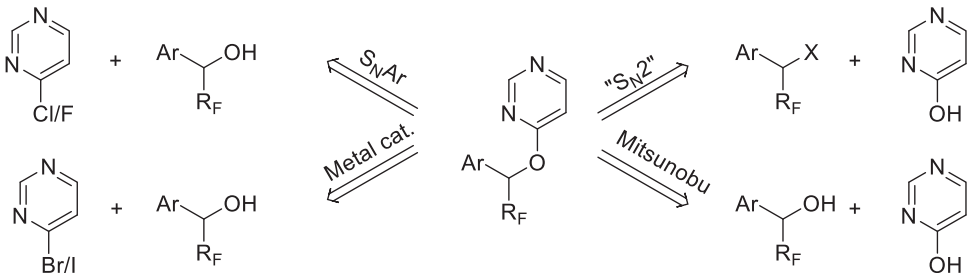
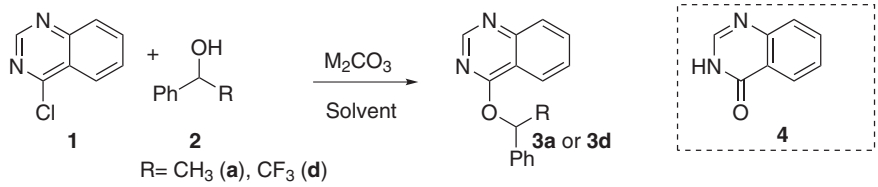


Scheme 1. Possible strategies to fluoro containing 4-alkoxypyrimidines.



Scheme 2. Nucleophilic aromatic substitution on 4-chloroquinazoline (**1**).

Solvent selections do not only depend on solubility of the reactants, but also on safety, effects on reaction rate, stability of the reagent and product, ease of work-up, pricing and environmental concerns [24,25]. However, solvent selection guidelines have been developed to aid the chemist in these sometimes difficult dilemmas [26]. Based on these guidelines we selected 2-methyl tetrahydrofuran (2-MeTHF), THF, acetonitrile, *tert*-butanol and water as interesting reaction media. In addition *N,N*-dimethylformamide (DMF) was included as a reference to conditions usually employed [27].

4-Chloroquinazoline (**1**) was first reacted in these six solvents at a scale of 100 mg in 2 mL solvent with either 1-phenylethanol (**2a**) or 2,2,2-trifluoro-1-phenylethanol (**2d**) as nucleophile and potassium or caesium carbonate as bases (2.5 equiv.), see Scheme 2. Reactions in water and DMF were performed at 90 °C, while for the other solvents reflux conditions were employed.

The degree of conversion and product distribution seen for the couplings in the various solvents with potassium carbonate are shown in Table 1. Using **2a** as nucleophile only processes in DMF gave a decent rate of reaction, and full conversion was reached in 5 h (Table 1, entry 4).

A mediocre degree of conversion was observed in acetonitrile and *t*-BuOH (entries 3 and 5), while no product were detected by GC when performing the substitution in 2-MeTHF or THF (entries 1–2). Reaction in water led to hydrolysis of the starting material yielding 4-hydroxyquinazoline (**4**) as the main product.

Substitutions of **1** with 2,2,2-trifluoro-1-phenylethanol (**2d**) in the presence of K_2CO_3 proceeded more readily also in the less polar solvents THF and 2-MeTHF (entries 7–8). Besides DMF also the use of acetonitrile and *t*-BuOH gave an acceptable rate of reaction for **2d** (entries 9–11). Given the higher nucleophilicity of 2,2,2-trifluoro-1-phenylethanol (**2d**) as compared to **2a**, the main product in water was **3d**. Overall, in the presence of K_2CO_3 the reaction rate depending on solvent followed the order DMF> acetonitrile> *t*-BuOH > >THF, 2-MeTHF. Water was concluded unsuited as solvent since the co-production of **4** leads to a more difficult purification process.

The results for the same transformations performed with Cs_2CO_3 as base are shown in Table 2. With 1-phenylethanol (**2a**) as nucleophile in Me-THF (Table 2, entry 1), full conversion could be obtained in 11 h, and even shorter reaction time was achieved with the more polar solvents (entries 2–5).

The increase in reactivity as compared to the use of K_2CO_3, can be accounted for by the higher solubility of the base, and the lower degree of solvation of the Cs-alkoxide [28,29]. Reactions with 2,2,2-trifluoro-1-phenylethanol (**2d**) as nucleophile under the same conditions proceeded with full conversion in less than one hour (entries 7–11). The use of water again gave **4** as a by-product in comparable amounts to that observed when using K_2CO_3. Overall, with Cs_2CO_3 as base the conversion rate depended less on the solvent used.

Table 1
Reaction of 4-chloroquinazoline (**1**) with alcohol **2a** and **2d** using 2.5 equivalents of potassium carbonate as base, scale: 100 mg **1** in 2 mL solvent.

Entry	Substrate	R	Solvent	Temp. (°C)	Time (h)	Conv.[a] (%)	Product(s)	Ratio 3/4
1	**2a**	CH_3	2-MeTHF	81	24	<1	**3a**	–[b]
2	**2a**	CH_3	THF	67	24	<1	**3a**	–[b]
3	**2a**	CH_3	CH_3CN	82	23	81	**3a**	>100
4	**2a**	CH_3	DMF	90	5	99	**3a**	>100
5	**2a**	CH_3	*t*-BuOH	82	23	63	**3a**	>100
6	**2a**	CH_3	Water	90	24	95[c]	**3a + 4**	11/89
7	**2d**	CF_3	2-MeTHF	81	19	>99	**3d**	>100
8	**2d**	CF_3	THF	67	19	>99	**3d**	>100
9	**2d**	CF_3	CH_3CN	82	1.5	>99	**3d**	>100
10	**2d**	CF_3	DMF	90	0.5	>99	**3d**	>100
11	**2d**	CF_3	*t*-BuOH	82	2	>99	**3d**	>100
12	**2d**	CF_3	Water	90	5	>99	**3d + 4**	87/13

[a] Conversion was measured by gas chromatography.
[b] No product was observed.
[c] Compound 4 was the main product.