Synthetic chemistry-led creation of a difluorinated biaryl ether non-nucleoside reverse transcriptase inhibitor†

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Received 13th September 2007, Accepted 24th September 2007
First published as an Advance Article on the web 2nd October 2007
DOI: 10.1039/b714091f

In the process of developing a series of novel, fluorinated biaryl ether NNRTIs, we fortuitously discovered derivative 20, which possesses excellent potency against both wild-type and clinically relevant mutations of the reverse transcriptase enzyme.

Introduction

Reverse transcriptase (RT) is an essential enzyme in the infectious life cycle of HIV and inhibition of this enzyme has shown great utility in the treatment of HIV. Unfortunately, established drugs called non-nucleoside reverse transcriptase inhibitors (NNRTIs), which bind in an allosteric pocket of the enzyme, are susceptible to viral resistance caused by single-point mutations in RT. As a result, there is still an unmet medical need for NNRTIs that do not suffer from rapid drug resistance.[1] Strategies have therefore focussed on developing NNRTIs that retain significant activity against the most clinically relevant mutations (particularly K103N and Y181C), which reduce their susceptibility to the mutant virus.

To this end we have worked on a series of biaryl ethers[2] that possess intrinsically high affinity for the RT enzyme and we desired a number of fluorinated derivatives to further build our structure–activity relationships (SARs) within this class, particularly with regards to their mutant profile. Fluorine imparts many desirable characteristics into drugs as it can modulate both the pharmacokinetic and pharmacodynamic properties of the compound.[3] Incorporating fluorine into molecules selectively and safely can represent a significant synthetic challenge and therefore methods for the generation of fluorinated 'fragments' are highly desirable. Our chemistry has focussed on the incorporation of fluorine into the B ring of the biaryl ether, and our originally planned targets are illustrated in Fig. 1. We discovered that during our synthetic exploits we were able to generate a pair of isomeric difluorinated NNRTIs (**3** and **20**), which possessed surprisingly different activities.

Results and discussion

Our initial target was the non-fluorinated derivative **1**, which would allow us to assess the effect, if any, of fluorinating ring B. **1** was prepared in three simple steps from 2-methoxy phenol **4** (Scheme 1). Arylation with commercially available 3-chloro-5-fluoro-benzonitrile provided the biaryl ether **6**. Treatment with boron tribromide revealed the phenol **8** which was subsequently alkylated with the known chloride **10**[2] to provide **1**. The fluorinated derivative **2** was prepared in the same manner using commercially available 5-fluoro-2-methoxy phenol **5** as starting material. Interestingly, although both **1** and **2** possess very good potency against the wild-type enzyme (Table 1), neither is capable of inhibiting the clinically relevant mutations K103N or Y181C to levels that are within ten-fold of the wild-type value.

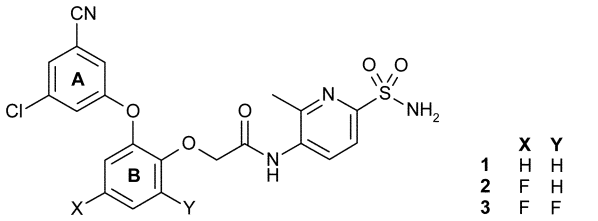
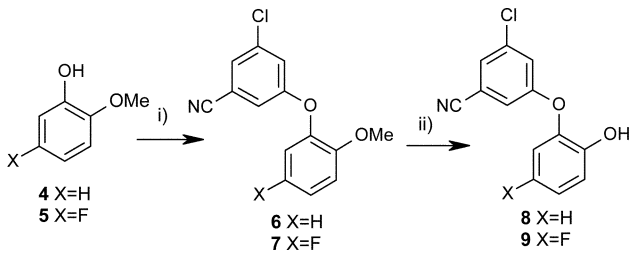
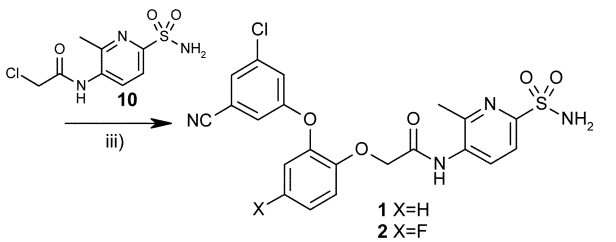


Fig. 1 Biaryl ether NNRTIs.





Scheme 1 *Reagents and conditions*: (i) 3-chloro-5-fluoro-benzonitrile, Cs_2CO_3, DMF, 80 °C, 28% (**6**), 100% (**7**); (ii) BBr_3, DCM, rt, 95% (**8**), 78% (**9**); (iii) **10**, K_2CO_3, NaI, DMF, 40 °C, 21% (**1**), 50% (**2**).

Table 1 Potency of **1** and **2** for wild-type, K103N and Y181C RT[a]

Compound	Wt IC_{50}/nM	K103N IC_{50}/nM	Y181C IC_{50}/nM
1	30	602	303
2	51	1510	533

[a] IC_{50} values are geomeans of 3 measurements.

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† Electronic supplementary information (ESI) available: Experimental details and COSY spectrum for compound **19**. See DOI: 10.1039/b714091f

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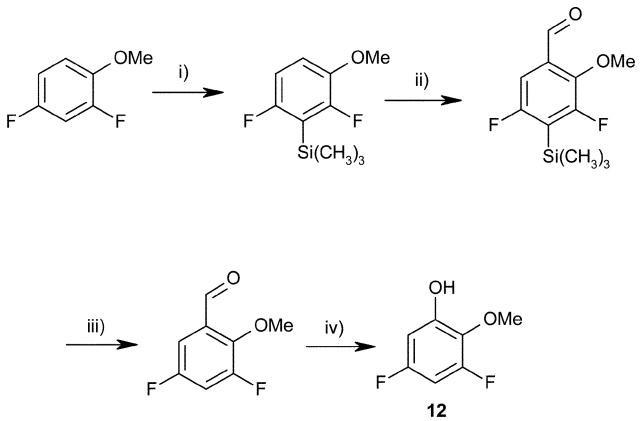
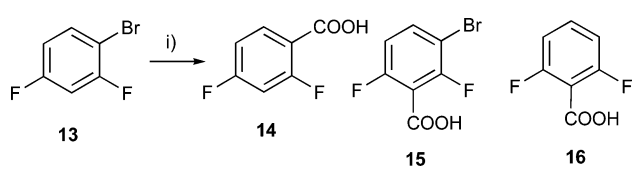
We further pursued difluorinated derivative **3** to build our SAR in this series. Using similar chemistry we planned to prepare **3** (Fig. 1) from the known phenol **12** which itself had been prepared previously in several steps from 2,4-difluoroanisole (Scheme 2).[4] This procedure relied on protecting the most acidic 3-position of 2,4-difluoroanisole with a trimethylsilyl group. We initially hypothesized that it may be possible to prepare intermediate **12** in a simpler manner *via* direct halogen–lithium exchange of commercially available 1-bromo-3,5-difluoro-2-methoxy benzene (**17**), quenching with an appropriate boronic ester followed by oxidation with hydrogen peroxide to provide the desired phenol **12**. Previous work by Schlosser and Heiss had suggested that this route would be feasible since treatment of 1-bromo-3,5-difluorobenzene with *n*-butyl lithium at −75 °C in THF followed by CO_2 gives 3,5-difluorobenzoic acid in 91% yield.[5]



Scheme 2 *Reagents and conditions*: (i) ^{n}BuLi, THF, −78 °C then $(CH_3)_3SiCl$, 94%; (ii) ^{n}BuLi, THF, −78 °C then DMF, 46% (7 : 1 ratio of *ortho* and *meta*-substituted aldehydes); (iii) TBAF, CF_3CH_2OH, THF, 43%; (iv) *m*CPBA, DCM then KOH aq. 64%.[4]

However, we were also aware of the work by Bridges *et al.*, which showed that treatment of the isomeric bromide **13** (Scheme 3) with *n*-butyl lithium at −78 °C followed by CO_2 can give a mixture of three products depending on the choice of solvent.[6] In diethyl ether, **13** gave **14** almost exclusively in 83% yield, but in THF **14**, **15** and **16** were formed in a ratio of 1 : 2 : 2 respectively and in 75% total yield. In this case an autometalation mechanism was proposed, whereby the initially formed organo-lithium can act as a base towards unlithiated substrate, extracting the most acidic proton (the 3-proton from the starting bromide) to give **14** and **15** upon quenching. This process consumes half an equivalent of *n*-butyl lithium, the remaining half is then available to deprotonate the reduced starting material, resulting in the formation of **16** upon quenching with CO_2.



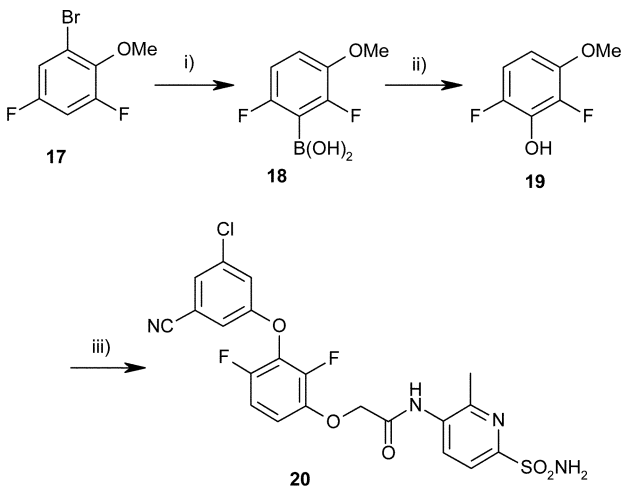
Scheme 3 *Reagents and conditions*: (i) ^{n}BuLi, THF or Et_2O, −78 °C then CO_2.[6]

Despite being a little unsure how the key step in our synthesis would proceed, we decided to pursue the halogen–lithium exchange chemistry with commercially available bromide **17** (Scheme 4). Interestingly, treatment of **17** with *n*-butyl lithium in THF, followed by a quench with triisopropyl borate and acid hydrolysis gave boronic acid **18** exclusively. Subsequent oxidation with hydrogen peroxide furnished the phenol **19** as the only regioisomer (proved by COSY NMR—see ESI†). Although we had not originally set out to prepare this isomer, we decided to push intermediate **19** through to the regioisomeric NNRTI using similar chemistry to that described above (Scheme 4). Fortuitously, derivative **20** possessed excellent potency against both wild-type RT and the K103N and Y181C mutants (Table 2).[7]

Table 2 Potency of **3** and **20** for wild-type, K103N and Y181C RT[a]

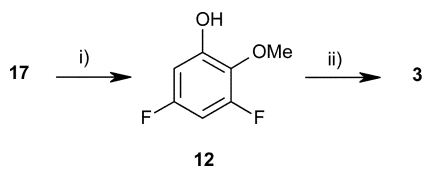
Compound	Wt IC_{50}/nM	K103N IC_{50}/nM	Y181C IC_{50}/nM
3	5450	67 300	45 100
20	4.3	12	19

[a] IC_{50} values are geomeans of 3 measurements.



Scheme 4 *Reagents and conditions*: (i) ^{n}BuLi, THF, −78 °C then $(iPrO)_3B$ then HCl aq., 43%; (ii) H_2O_2 aq., AcOH, THF, rt, 59%; (iii) a. 3-chloro-5-fluoro-benzonitrile, Cs_2CO_3, DMF, reflux, 34%, b. BBr_3, DCM, rt, 50%, c. **10**, K_2CO_3, NaI, DMF, 40 °C, 84%.

We still desired a method of preparing our original difluorinated isomer **3**, particularly one which avoided the route outlined in Scheme 2 to intermediate **12**. Following the precedence set by Bridges, we then repeated the halogen–lithium exchange chemistry on bromide **17** in diethyl ether (Scheme 5). Pleasingly, treatment of the resulting boronic acid with hydrogen peroxide provided the desired phenol **12** exclusively. Arylation, demethylation and alkylation follows the same chemistry described previously to



Scheme 5 *Reagents and conditions*: (i) a. ^{n}BuLi, Et_2O, −78 °C then $(iPrO)_3B$ then HCl aq., b. H_2O_2 aq., AcOH, THF, rt, 62% over two steps; (ii) a. 3-chloro-5-fluoro-benzonitrile, Cs_2CO_3, DMF, reflux, 75%, b. BBr_3, DCM, rt, 70%, c. K_2CO_3, NaI, DMF, 40 °C, 40%.

provide the difluorinated derivative **3**. Interestingly, this derivative was over 1000-fold less potent than its isomer **20** (Table 2).

Conclusions

We have developed short synthetic routes to successfully furnish fluorinated biaryl ether NNRTIs.[8] Halogen–lithium exchange chemistry led to an alternative arrangement of substituents on ring B of the biaryl ether, resulting in the preparation of the difluorinated derivative **20**, which possesses excellent potency against the wild-type RT enzyme and retains impressive activity against the clinically relevant mutations K103N and Y181C. This fortuitous discovery illustrates the essential role synthetic chemistry has to play in the drug discovery/design process. Further development of **20**, and a detailed structure–function analysis of this series, is ongoing work within our group and will be reported in due course.

Acknowledgements

We thank Romu Corbau, Ian Burr, Alex Martin and Amy Thomas for determining the potencies of these compounds. We also thank Torren Peakman for performing the COSY NMR on **19**.

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8 All compounds (**1**, **2**, **3** and **20**) are non-cytotoxic, *i.e.* $CC_{30} > 30\ \mu M$.