Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5930

www.rsc.org/obc

COMMUNICATION

Expeditious one-pot synthesis of C3-piperazinyl-substituted quinolines: key precursors to potent c-Met inhibitors†

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Received 26th May 2011, Accepted 1st July 2011
DOI: 10.1039/c1ob05830d

An effective one-pot synthesis of quinolines bearing diverse C3-piperazinyl functions was developed by using a modified Friedländer's protocol. The method not only enables the synthesis of our early reported c-Met inhibitor on a large scale, but also provides a way to generate novel multi-substituted quinolines for further structure–activity relationship (SAR) study.

The bicyclic quinoline scaffold is an important structure core widely embedded in both bioactive natural products[1] and synthetic therapeutic agents.[2,3] Although the typical method to prepare quinoline system was reported by Friedländer in 1882,[4] and has been widely used as one of the most convenient routes to assemble the scaffold, new process to readily construct quinolines, especially those with multi-substitutions, is still highly needed. In general, Friedländer synthesis involves condensation of an α-amino carbonyl compound (*e.g. o*-aminobenzaldehyde, or 1-(*o*-aminophenyl)ethanone) with a ketone or aldehyde under either basic or acidic condition. Following such procedure, variant C3-alkyl, C3-alkyloxy, or C3-aryl substituted quinolines were easily realized recently by treating *o*-aminoarylcarbaldehyde with an appropriately substituted aldehyde or ketone.[5,6] However, to the best of our knowledge, there is no report on the synthesis of C3-amino substituted quinolines using Friedländer's one-pot synthetic procedure.

Most of current reported 3-amino-quinolines were prepared[5,7] either by C-N coupling of quinolin-3-yl halides with corresponding amino substrates, or by direct reduction of 3-nitro-quinolines. These methods generally suffered from poor yields or limited substrate scope. For example, we recently reported[8] the synthesis of a series of 3,5,7-tri-substituted quinolines among which the lead compound **1** bearing a C3-amino group showed very high potency to the receptor tyrosine kinase (RTK) c-Met[9] with an IC_{50} value of 0.93 nM and exerted promising *in vivo* antitumor activity. Initially, compound **1** was synthesized by palladium-catalyzed C–N coupling of bromide **2** and *N*-methylpiperazine (Fig. 1, path a), but the reaction turned out to be extremely sluggish and afforded compound **1** in trace yield (~5%). Alternatively, we switched the reaction sequences by introducing the C3-amino group, prior to the installation of the C5-benzylamino substituent (Fig. 1, path b) leading to the final product **1** obtained in 48% overall yield.[8] However, the method is far beyond practicality since preparation of 3-bromoquinoline **4** proved to be extremely difficult. In view of the significant antitumor potency of compound **1**, it is urgent for us to establish a pratical method to readily access the polysubstituted quinoline skeleton either to provide **1** on a large scale for preclinical study or to construct a diversified library to generate more potent c-Met inhibitors. Herein, in the current communication, we report an improved version of Friedländer's quinoline synthesis to readily access multi-substituted quinolines bearing a C3-piperazinyl substituent.

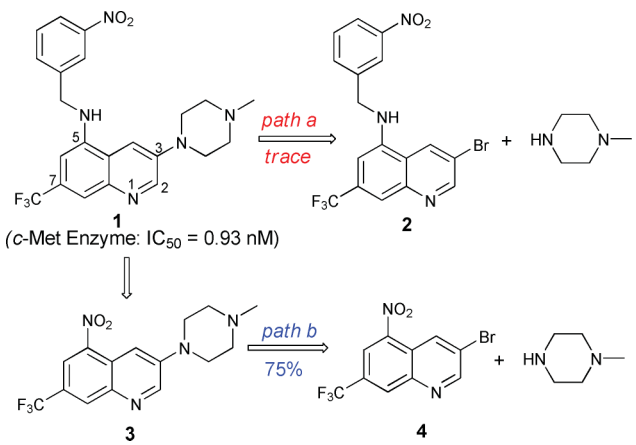

Fig. 1 Our earlier synthesis of quinoline **1**.

First, we prepared *o*-aminoarylcarbaldehyde **9**, the Friedländer's substrate by using literature procedures as described in Scheme 1. Regioselective reduction[10] of 2-methyl-1,3-dinitro-5-(trifluoromethyl) benzene (**5**) afforded 2-methyl-3-nitro-5-(trifluoromethyl)aniline (**6**) in 92% yield. Diazotization[11] of aniline **6**, followed by bromination with CuBr yielded bromide **7** in 86% overall yield. Treating[12] bromide **7** with DMF·DMA followed by $NaIO_4$ afforded aldehyde **8** in

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob05830d

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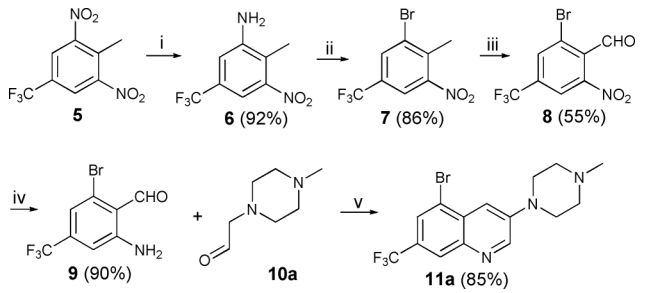


Reaction conditions: i) $(NH_4)_2S$, EtOH, reflux; ii) a $NaNO_2$, HBr/H_2O; b CuBr, HBr, reflux; iii) a DMFDMA, DMF, reflux; b $NaIO_4$, DMF/H_2O; iv) Fe, NH_4Cl, $EtOH/H_2O$; v) NaOH, EtOH, reflux.

Scheme 1 Synthesis of quinoline **11a**.

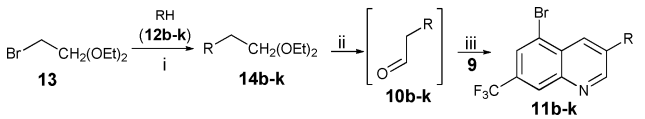
55% overal yield. After reduction with Fe/NH_4Cl, 2-amino-6-bromo-4-(trifluoromethyl)benzaldehyde **9** was obtained in 90% yield.

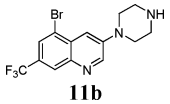
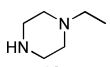
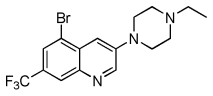
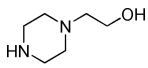
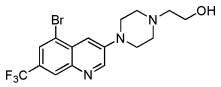
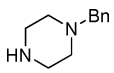
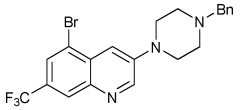
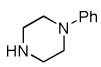
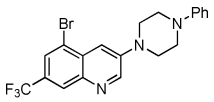
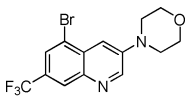
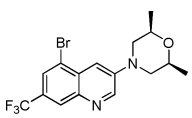
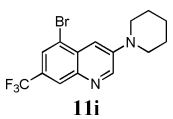
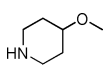
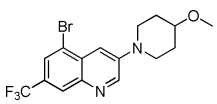
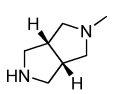
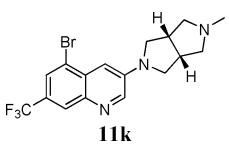
With Friedländer substrate **9** in hand, quinoline synthesis was conducted by treating **9** with 2-(4-methylpiperazin-1-yl)acetaldehyde (**10a**) in refluxed EtOH in the presence of NaOH.[6b,6c,13] To our delight, the reaction proceeded smoothly, and quinoline **11a**, the key precursor to the c-Met inhibitor **1**, was obtained in 85% yield. It was found that other bases such as KOH and NaOEt also promoted the reaction and afforded quinoline **11a** in 78 and 82% yield, respectively.

With success in synthesis of quinoline **11a**, we further explored the substrate scope by introducing diverse substituents to the piperazin-4-yl fragment. Therefore, various 2-(4-substituted-piperazinyl)acetaldehydes **10b–k**, either obtained from commercial source or prepared *in situ* by hydrolysis[14] of 1-(2,2-diethoxyethyl)piperazines **14b–k**, were employed to react with 2-amino-benzaldehyde **9**. As described in Table 1, all the reactions went through smoothly and yielded the expected 3-amino-5-bromo-7-trifluoromethyl quinolines **11b–k** in 74-89% yield. It is of note that *N*-acetyl substituted substrate **10b** did not tolerate the strong basic reaction condition, and *N*-deacylated product **11b** was obtained in 76% yield (Table 1, entry 1). Indeed, the result provided an additional option for further structural derivation on the NH-site. *N*-Hydroxyethyl substituted substrate (entry 3) participated in the reaction as well without additional protection, and product **11d** was obtained in 86% yield which is very useful for further functional transformation. More sterically substituted aldehydes **10e** and **10f** (entries 4 and 5) did not have significant impact to the reaction yields, compared to the less steric substrates **10c**, **10g**, **10i**, and **10j** (entries 2, 6, 8 and 9). Interestingly, through the protocol, quinolines **11h** and **11k** bearing a chiral fragment were also easily prepared in 89% and 74% yield, respectively (entries 7 and 10).

With the encouraging results obtained above, we turned out to prepare synthetically more challenging 3-amino-quinolines bearing a C2-substituent. First, Friedländer-type ketone, 1-(4-methylpiperazin-1-yl)propan-2-one (**16a**) was prepared[14] from 1-bromopropan-2-one (**15**) and *N*-methylpiperazine (Scheme 2). Subsequent quinoline synthesis was conducted by treating ketone **16a** with *o*-aminoarylcarbaldehyde **9** following a similar procedure described above. Quite disappointingly, the expected 2-methyl-3-aminoquinoline **17a** was obtained in 23% yield, along with 2-substituted quinoline **18** in 61% yield (entry 1, Table 2). The low yield in producing **17a** is likely due to the steric effect of

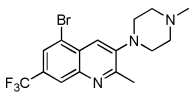
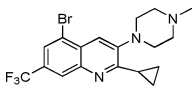
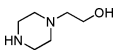
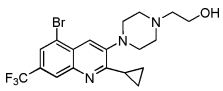
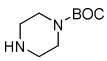
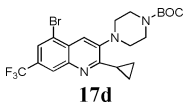
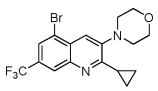
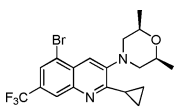
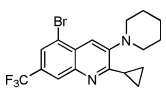
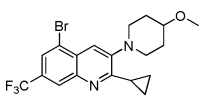
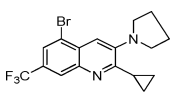
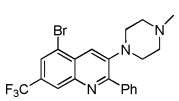
Table 1 Synthesis of 3-aminoquinolines **11b–k**



Entry	RH	Product	Yield
1	 **12b**	 **11b**	76%
2	 **12c**	 **11c**	85%
3	 **12d**	 **11d**	86%
4	 **12e**	 **11e**	75%
5	 **12f**	 **11f**	83%
6	 **12g**	 **11g**	89%
7	 **12h**	 **11h**	89%
8	 **12i**	 **11i**	84%
9	 **12j**	 **11j**	88%
10	 **12k**	 **11k**	74%

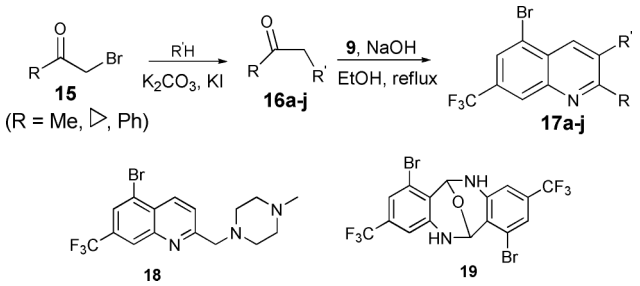
Reaction conditions: i) K_2CO_3, KI, acetone, reflux; ii) *con.* HCl in MeOH, reflux; iii) NaOH, EtOH, reflux

Table 2 Synthesis of 2,3-bisubstituted quinolines

Entry	*R*	R′H	Product	Yield (%)
1	Me		 **17a**	23(61[a])
2	▷		 **17b**	67(8[b])
3	▷		 **17c**	68(7[b])
4	▷		 **17d**	61(9[b])
5	▷		 **17e**	65(8[b])
6	▷		 **17f**	66(6[b])
7	▷		 **17g**	67(7[b])
8	▷		 **17h**	69(6[b])
9	▷		 **17i**	64(10[b])
10	Ph		 **17j**	15(40[b])

[a] Yield of quinoline **18**. [b] Yield of diazabicyclo[3.3.1]nonane **19**.

piperazine moiety in **16a** thus leading to quinoline **18** formed from the less steric side as the major product. To limit the production of **18**, we envisioned that replacing the methyl in **16a** with a more bulky group would force quinoline ring forming from piperazinemethyl side and yield the expected 2,3-bis-substituted quinolines (*e.g.***17a**) as the major product. Therefore, cyclopropyl ketones **16b–i** were prepared[14] by



Scheme 2 Synthesis of 2,3,5,7-penta-substituted quinolines.

treating 2-bromo-1-cyclopropylethanone with an appropriate *N*-substituted piperazine.

As expected, the subsequent quinoline synthesis of ketones **16b–i** with *o*-aminoarylcarbaldehyd **9** led to 2-cyclopropyl-3-piperazinylquinolines **17b–i** formed as the major products in 61–69% yield (entries 2–9, Table 2). It is of note that a minor side product **19**, formed by dimerization of *o*-aminoarylcarbaldehyde **9**, was also obtained in each of the reactions in less than 10% yield (Scheme 2, Table 2). The self-dimerization of aldehyde **9** was a competitive reaction and can be enhanced significantly when a much bulkier substrate **16j** was used (entry 10). In such case, 9-oxa-2,6-diazabicyclo[3.3.1]nonane **19** was produced as the major product, and the 2,3-bis-substituted quinoline **17j** was obtained in only 15% yield.

With the key precursor 5-bromo-3-aminoquinolines **11a–k** and **17a–j** in hand, we decided to explore the practicality in preparation of the target c-Met inhibitors. First, lead compound **1** was prepared by coupling 5-bromo-3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl) quinoline (**11a**) with 3-nitrobenzylamine under $Pd_2(dba)_3$/BINAP/Cs_2CO_3 catalytic system[8] To our delight, the reaction went though nicely and provided target compound **1** in 75% yield. More importantly, we synthesized the product on multi-gram scale with nearly identical yield that warranted for further biological profiling of the potent c-Met inhibitors.

Meanwhile, a series of new c-Met inhibitors **21a–k** were designed by merging the 3-aminoquinoline core of **1**[8] and triazolopyridazine core of **20**,[15] another potent c-Met inhibitor reported by Amgen, into one molecule (Fig. 2). As described in Table 3, a small class of triazolo[4,3-b]pyridazin-3-ylmethanamines **22a–j** bearing diverse C-6 functions were prepared first,[15] and then subjected to $Pd_2(dba)_3$-catalyzed C–N coupling with 5-bromoquinoline **11a** or **17b** following a similar procedure[8] as described for preparation of **1**. The expected multi-substituted quinolines **21a–k** were obtained in 63–83% yield (entries 1–11, Table 3).

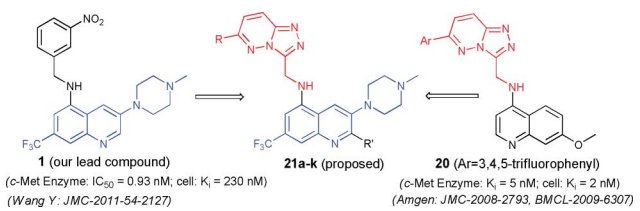
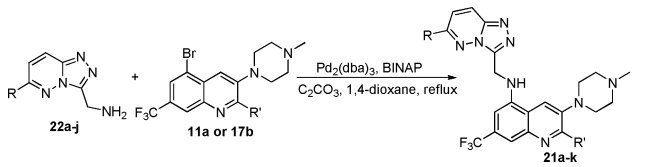


Fig. 2 Design of novel c-Met inhibitors **21a–k**.

The newly synthesized quinolines **21a–k** were evaluated for their ability to inhibit c-Met enzymatic activity using our reported procedure.[8] As summarized in Table 3, all the C2 non-substituted quinolines **21a–j** (entries 1–10) displayed sub-nanomolar

Table 3 Synthesis and c-Met enzymatic activity of quinolines **21a–k**



Entry	*R*	R′	Yield	IC_{50} (μM)[a]
1 (**21a**)	H	H	80%	0.33
2 (**21b**)	Cl	H	63%	0.03
3 (**21c**)	Me	H	78%	0.22
4 (**21d**)	MeO	H	75%	0.12
5 (**21e**)	EtO	H	79%	0.40
6 (**21f**)	Me_2N	H	74%	0.28
7 (**21g**)	Ph	H	83%	0.16
8 (**21h**)	2-thienyl	H	81%	0.08
9 (**21i**)	2-furyl	H	79%	0.07
10 (**21j**)	1-Me-pyrazol-4-yl	H	78%	0.28
11 (**21k**)	1-Me-pyrazol-4-yl	cyclopropyl	71%	4.4
1[b]	—	—	—	0.00093

[a] *In vitro* kinase assays were performed with the indicated purified recombinant c-Met kinase domains, IC_{50}s were calculated by Logit method from the results of at least three independent tests with six concentrations each. [b] Our previously reported[8] c-Met inhibitor

inhibitory activity at the c-Met enzyme, while quinoline **21k** bearing a C2-substituent did not show appreciable activity. It was found that compounds containing a small electron-donating substituent at the C6 of the triazolopyridazine fragment showed similar IC_{50} values in 0.1~0.4 μM range (entries 1,3–6). Higher potency was observed on compounds **21b**, **21h** and **21i** possessing IC_{50} values less than 100 nM. Overall, all these compounds were much less potent, in comparison to the parent compound **1**. However, in view of the higher cellular activity[15] of the triazolopyridazine-containing compound **20**, compound **1** only showed moderate activity in the cell indicating that triazolopyridazine analogues may have better cell permeability. Therefore, these compounds will be subjected to further cellular biological assay.

In summary, we have developed a highly effective one-pot synthetic strategy to access 3-amino-quinolines by using a modified Friedländer's protocol. A series of novel multi-substituted quinolines bearing diverse C3-piperazinyl functions were synthesized in good yields. Such method not only enables the synthesis of our early reported c-Met inhibitor on a large scale, but also provides a way to generate novel quinolines with multi-substituents for further structure–activity relationship (SAR) study.

Acknowledgements

The authors are grateful to Shanghai Commission of Science and Technology (10410702600, 10JC1417100, 10dz1910104), National Science & Technology Major Project on "Key New Drug Creation and Manufacturing Program" (2009ZX09301-001, 2009ZX09103-062), the Natural Science Foundation of China for Distinguished Young Scholars (No 30725046), and Program of Shanghai Subject Chief Scientist (No 10XD1405100).

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