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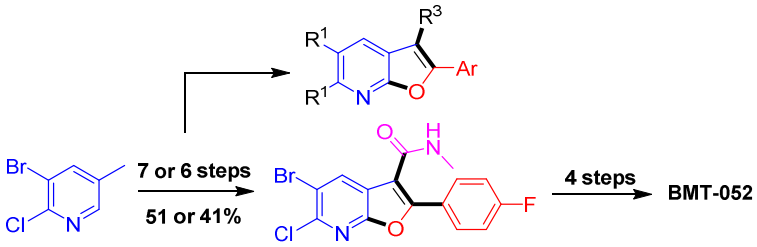
Graphical Abstract



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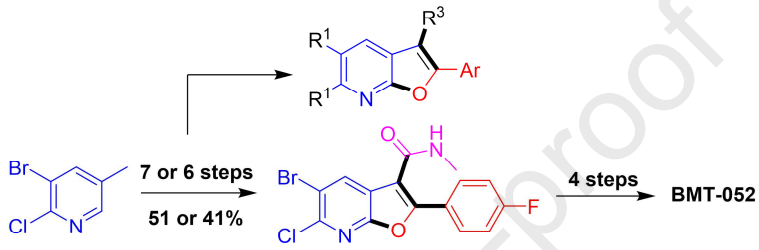

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ABSTRACT

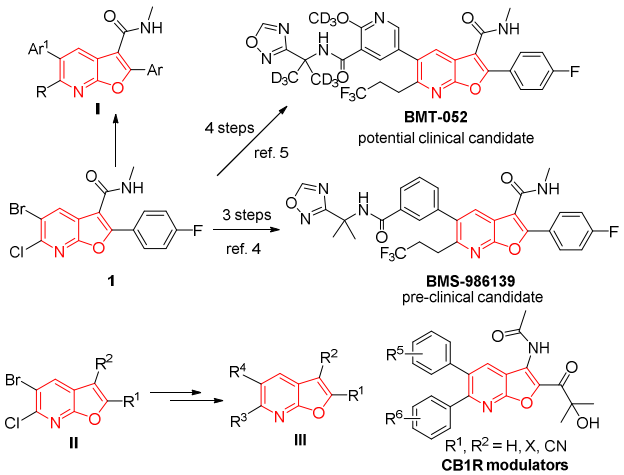
A series of tetrasubstituted 7-azabenzofurans displays remarkable pan-genotype inhibition of HCV NS5B polymerase. One of them has been identified as a potential clinical candidate. Completely different from the original synthesis of a common and key intermediate for this class of compounds, two novel and improved synthetic approaches are developed. Almost every step of the synthesis has been optimized, including several important but not fully explored transformations, such as radical bromination with methyl pyridine and cyanide substitution with TMSCN. The 7-azabenzofuran core is prepared by an acylation-heterocyclization reaction, using acyl chloride as both the reactant and the activation reagent for the *N*-oxide substrate. Compared with the BMS synthesis, the overall yield has been tripled, and those harmful or cost-effective synthetic steps have been reduced. Furthermore, a transition-metal-free synthetic method for the construction of 3-cyano substituted 7-azabenzofurans is presented.

1. Introduction

Hepatitis C virus (HCV) is a serious disease endangering human health with high mortality and morbidity. It initiates critical liver malfunction like cirrhosis, hepatocellular carcinoma or liver HCV cancer. Though the vaccine therapy for prototypes of Hepatitis A and B is available, vaccination program to combat Hepatitis C is still in progress. The treatment has been progressed rapidly,[1] but morbidity and mortality rates are still predicted to rise, efficacious and tolerable therapies are urgently needed. It has become the bottleneck problem in treating this disease that the appropriate treatment regimen and duration can vary depending on the patient's viral genotype.[2] Therefore, the development of pan-genotypic NS5B polymerase inhibitors is the ideal regimen in treating HCV.

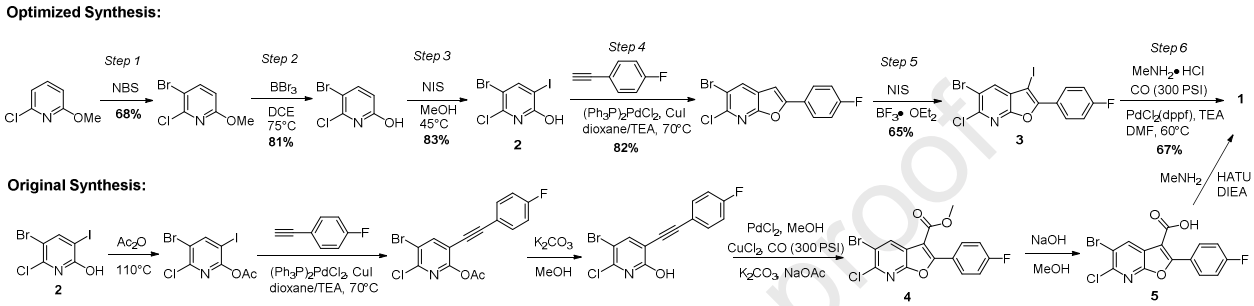
In 2014, BMS scientists reported a series of novel tetrasubstituted 7-azabenzofurans (**I**, Scheme 1) exhibiting pan-genotype inhibition of HCV NS5B polymerase.[3] After extensive SAR studies, BMS-986139 was selected as a preclinical candidate.[4] Unfortunately, it becomes ineffective in phase I due to microcrystallization problems in toxicological studies. Further studies led to the identification of the second generation of pan HCV NS5B polymerase inhibitors i. e., BMT-052 as a potential clinical candidate, which is able to overcome the poor metabolic stability of the previous analogues and has escalating inhibition.[5]

Scheme 1. Compound **1** as the Common and Key Intermediate for Bioactive 7-Azabenzofurans.



Compound **1**, a 5-bromo-6-chloro substituted 7-azabenzofuran, attracts our attention. It is not only the common and key intermediate for this class of HCV NS5B polymerase inhibitors, but also can be converted to various bioactive 7-azabenzofurans. As shown in Scheme 1, BMT-052 is prepared from **1** in 4 steps by simply replacing the bromo and chloro atoms.[5] Similarly, BMS-986139 is prepared in 3 steps.[4] Besides, a more general form **II** can be accessed by a similar synthetic approach to **1**. The C6-chloro atom can be easily substituted by various amines, alcohols, thiols, *et al.* through S_NAr, or both the C5-bromo and C6-chloro atoms can be substituted by aryl and alkyl groups via metal catalyzed cross coupling reactions to afford those biologically active 7-azabenzofuran **III**. One of the good examples can be found with CB1R modulators.[6] Therefore, the efficient and facile synthesis of **1** not only offers large scale production of this series of compounds, but also provides access to various tetrasubstituted 7-azabenzofurans.

Scheme 2. Route 1-BMS Synthesis of Compound **1**.



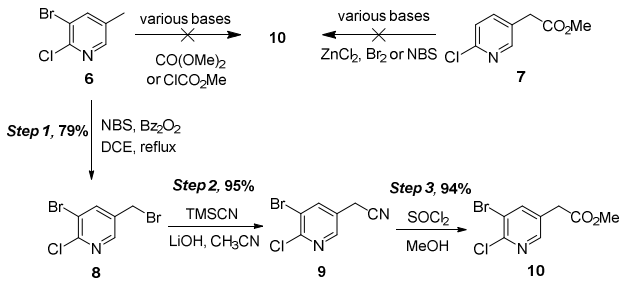
Although **1** is relatively small in size, the construction of 7-azabenzofuran core and the presence of four substituents, especially the two reactive halogen atoms make it a quite challenging synthetic problem. BMS scientists developed two approaches to **1** (Scheme 2). The optimized synthesis requires 6 steps with an overall yield of 16%,[4] and the original one is longer (9 steps in total, 6 steps from **2**) and tedious.[3b] The low total yield renders this synthetic route not practical in the large scale production of the final target. Besides, there are many drawbacks in this synthesis from green chemistry standpoint. First, too many halogenating reagents were used in the synthesis. The synthesis commenced with 2-chloro-6-methoxypyridine, and halogenating reagents, such as NBS, BBr_3 and NIS were used in every step of the first five steps. The use of these halogenating reagents is not only harmful to the environment, but also is wasted as the three halogen atoms in **3** are all substituted by carbon or nitrogen atoms finally. Second, one third of the reactions were catalyzed by Pd catalysts. This not only increases the cost, but also causes environmental problems. Finally, the highly toxic CO gas was used in the last step, and high-pressure operation (300 psi) was required.

Our group is particularly interested in the preparation of biologically active complex pyridine derivatives based on pyridine *N*-oxides chemistry,[7] which has been demonstrated to be a powerful and versatile strategy for direct incorporation of new functionalities at the C-2 position.[8] We recently reported the efficient synthesis of a compound with structure **I**,[9] but this route cannot be applied to BMT-052. In order to solve the aforementioned problems associated with this class of compounds, we reported herein a practical, scalable and greener synthesis of compound **1**.

2. Results and Discussion

We were initially focused on the synthesis of pyridine-3-acetate **10** (Scheme 3), which is the appropriate substrate for Emery's synthesis of 3-ester substituted 7-azabenzofuran.[10] We explored several routes and we finally envisioned attachment of an ester group to inexpensive and readily available 3-bromo-2-chloro-5-methylpyridine (**6**, Sigma Aldrich price: $56.10/25g[11]). Attempt conversion of the dihalide **6** to **10** by benzylic deprotonation[12] with various bases and alkylation with dimethyl carbonate or methyl chloroformate resulted in vain. Bromination of metalated **7** via Li-Zn transmetalation[13]

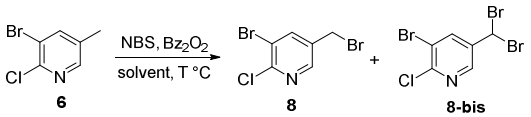
Scheme 3. Route 2-Synthesis of the Advanced Intermediate **10**.



did not yield **10** either. Then, a three-step synthesis of **10** was developed. Although CCl_4 is a common solvent for radical bromination, the yield is not satisfactory for those N-heterocyclic compounds.[14] The optimization of this reaction is carried out. Initial attempts to effect benzylic bromination of **6** with NBS in acetonitrile under the catalysis of benzoyl peroxide afforded **8** in only 32% yield (entry 1, Table 1). The dibrominated byproduct **8-bis** was detected, and lots of **6** remained unreactive. Stronger conditions were applied, including higher reaction temperature in a sealed tube, more benzoyl peroxide and more concentrat-

ed reaction media, but did not afford essential difference (entries 2-4). In order to reduce the formation of **8-bis**, less NBS was employed. Although the reaction was still incomplete, the yield improved to 73% (entry 5). However, further reducing the quantity of NBS was harmful to the reaction (entry 6). Next, screening of the solvent led to the identification of DCE as the best one (entries 7-10). Although the yield is similar to CH_3CN, DCE is preferred due to the less toxicity. Incomplete reaction resulting in lower yield was detected utilizing less NBS (entry 11). This reaction is scalable. The yield of 5.0 g scale is slightly higher than that of 0.2 g scale (entry 12).

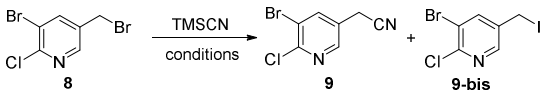
Table 1. Optimization of the radical bromination.*



entry	solvent	eq. of NBS	T (℃)	yield (%)
1	CH_3CN	3.0	reflux	32
2	CH_3CN	3.0	100	54
3[a]	CH_3CN	3.0	reflux	45
4[b]	CH_3CN	3.0	reflux	40
5	CH_3CN	1.5	reflux	73
6	CH_3CN	1.1	reflux	70
7	CCl_4	1.5	reflux	50
8	THF	1.5	reflux	0
9	dioxane	1.5	reflux	0
10[c]	DCE	1.5	reflux	75
11[d]	DCE	1.1	reflux	71
12[e]	DCE	1.5	reflux	79

*Unless otherwise noted, all reactions were conducted with **6** (200 mg, 1.0 equiv), Bz_2O_2 (0.1 equiv) and NBS in solvent (0.34 M). [a] 0.2 equiv of Bz_2O_2 was used. [b] More concentrated solution (0.68 M) was applied. [c] The reaction is complete in 6 hours. [d] About 20% of compound **6** remained unreactive after 10 hours of reaction. [e] 5.0 g of **6** was used.

Table 2. Optimization of the benzylic cyanation.*



entry	additive/eq.	eq. of TMSCN	solvent	T°C	yield (%)
1	KI/0.2 + K_2CO_3/2.0	2.0	CH_3CN	25	0
2	KI/0.2 + K_2CO_3/2.0	2.0	acetone	25	0
3	KI/0.2 + K_2CO_3/2.0	2.0	DMF	25	0
4	KI/0.2 + K_2CO_3/2.0	2.0	acetone	reflux	0
5	TBAF/1.5	1.5	CH_3CN	25	39
6	LiOH/1.2	1.2	CH_3CN	25	93
7[a]	LiOH/1.2	1.2	CH_3CN	25	95

*Unless otherwise noted, all reactions were conducted with **8** (100 mg, 1.0 equiv), additive and TMSCN in solvent (0.25 M). [a] 5.41 g of **8** was used.

Compound **8** was then proceeded to the next step. Although substitution of benzyl bromide with cyanide by KCN or NaCN is well documented, the use of much less toxic TMSCN is relatively underexplored. Following a known procedure under basic conditions and the catalysis of KI,[15] lots of starting material remained without detecting the desired product **9**. Obtained instead was the iodide substituted **9-bis** (entry 1, Table 2). Switching the reaction solvent to acetone or DMF, or increasing reaction temperature did not afford **9** either (entries 2-4). Failure to perform this reaction may be rationalized by the weaker nucleophilicity of TMSCN. Strategies that could enhance the nucleophilicity of TMSCN was then tested. TBAF or LiOH was selected as both of them could initiate silicon-carbon cleavage, generating cyanide ion to promote the reaction. Gratifyingly, both reagents produced **9** (entries 5 & 6), and LiOH afforded excellent yield (entry 6). Moreover, this condition was also successfully applied to 5.4 g scale reaction (entry 7). Hydrolysis of **9** in methanol afforded **10** in 94% yield (Scheme 3). Fortunately, the C2-chloro atom survived and not substituted by methoxy or hydroxy group.

We envisioned that cyanide **9** as a possible precursor for the construction of 7-azabenzofuran core, which would lead to a more concise synthesis of **1** than starting from **10**. **9** was oxidized by peroxytrifluoroacetic acid, generated *in situ* by reaction of urea hydrogen peroxide with TFAA, to give pyridine *N*-oxide **11** cleanly and quantitatively (Scheme 4)**.** Due to the similar electron withdrawing character of cyano group and ester group, it was expected that the cyano substituted 7-azabenzofuran **12** would be produced in high efficiency by subjecting **11** to the acylation-heterocyclization conditions developed by Emery.[10] However, lots of **11** remained and **12** was obtained in only 18% yield (entry 1, Table 3). Switching DCM to chloroform and heating the reaction to reflux gave similar result (entry 2). The acylation reaction is the rate determining step, therefore faster deprotonation by a stronger base may offer better result. After careful screening of bases and solvents, LiHMDS was identified as the best choice (21% yield, entry 8). Doubling the amount of THF and increasing the quantity of acyl chloride afforded better result (entry 9). To our delight, the yield was almost doubled by doubling the quantity of LiHMDS (entry 10), but further increase of LiHMDS was harmful to the reaction (entry 11). Finally, we found that the yield could be increased to 63% by adding 1.0 equiv of DMAP to the reaction mixture, which also resulted in easier isolation of the product from the large excess of 4-fluorobenzoyl chloride. Moreover, similar result was achieved for larger scale reaction (59% yield for 4.40 g scale, see Experimental Section). Switching the base to LDA led to worse result (entry 13).

Scheme 4. Attempt Synthesis of **1** and **4** from Cyanide Precursor.

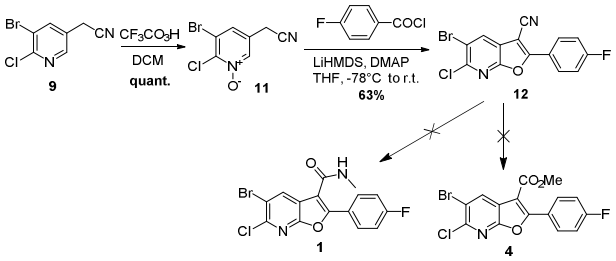
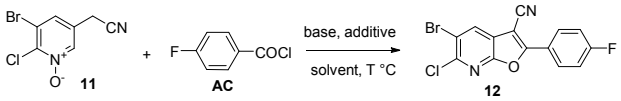


Table 3. Optimization of the acylation-heterocyclization with cyanide substrate.*

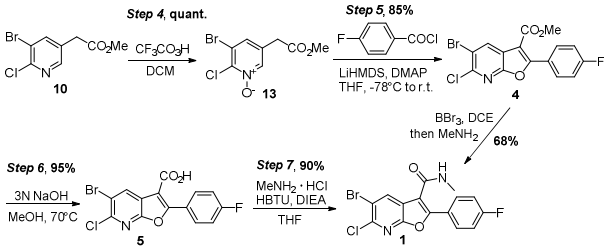


entry	base	eq. of DMAP	eq. of AC	solvent	yield (%)
1[a]	DBU	6 equiv	6.0	DCM	18
2[a,b]	DBU	6 equiv	6.0	$CHCl_3$	15
3[c]	NaH	none	2.0	THF	0
4[c]	NaH	none	2.0	toluene	0
5[c]	NaH	none	2.0	DMF	0
6[c]	$NaNH_2$	none	2.0	THF	5
7[c]	^{t}BuOK	none	4.0	THF	0
8[c]	LiHMDS	none	2.0	THF	21
9	LiHMDS	none	6.0	THF	30
10[d]	LiHMDS	none	6.0	THF	56
11[e]	LiHMDS	none	6.0	THF	45
12[d]	LiHMDS	1 equiv	6.0	THF	63
13	LDA	1 equiv	6.0	THF	42

*Unless otherwise noted, all reactions were conducted with *N*-oxide (100 mg, 1.0 equiv), base: DBU (1.2 equiv) / LiHMDS (1.1 equiv) / NaH (1.2 equiv) / $NaNH_2$ (1.2 equiv)/ ^{t}BuOK (1.2 equiv)/ LDA (2.2 equiv), additive, and AC in solvent (0.125 M) at r.t. [a] 0.17 M concentration was applied. [b] The reaction was heated to reflux. [c] 0.25 M concentration was applied. [d] 2.2 equiv of LiHMDS was used. [e] 4.0 equiv of LiHMDS was used.

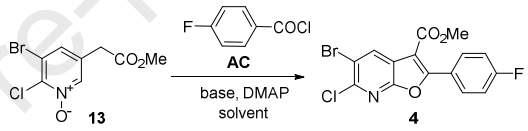
With the advanced intermediate **12** in hand, it seems that the following transformation to **1** is straight forward (Scheme 4). Unfortunately, this synthetic route is not feasible. Attempts to convert **12** directly to primary amide **1** by modified Ritter reaction procedure[16] were unsuccessful. Alongside the Ritter reaction, we simultaneously pursued the hydrolysis of **12** to **4**. However, following the procedure of the transformation from **9** to **10** did not produce the desired product.

Scheme 5. Route 2-Completion of the Synthesis.



Finally, the advanced intermediate **10** was selected and elaborated to **1** successfully by two efficient routes (Scheme 5). **10** was oxidized to afford **13** in quantitative yield without the need of any column purification. Compound **13** was then subjected to the acylation-heterocyclization conditions, and the tetrasubstituted 7-azabenzofuran **4** was obtained in 85% yield after extensive studies (Table 4). Completion of the synthesis was accomplished by an ester hydrolysis and HBTU-mediated coupling between **5** and tert-butylamine with above 90% yield for both steps. Intermediate **4** was also proceeded to the ester aminolysis step to explore a more concise synthesis of **1**. Original attempts to perform this reaction using $MeNH_2$ under various basic conditions did not yield any desired product, neither did $AlMe_3$[17] nor $Mg(OMe)_2$,[18] which have been reported very effective for amidation of esters. Running the reaction with BBr_3, another effective ester aminolysis reagent,[19] afforded the desired product **1** in 68% yield (Scheme 5). Further optimization did not give any satisfactory result.

Table 4. Optimization of the acylation-heterocyclization with ester substrate.*



entry	eq. of LiHMDS	eq. of DMAP	eq. of AC	yield (%)
1	2.2	1.0	6.0	65
2	1.1	1.0	6.0	86
3	1.1	none	6.0	78
4	1.1	1.0	4.0	79
5[a]	1.1	1.0	6.0	68
6[b]	1.1	1.0	6.0	85

*Unless otherwise noted, all reactions were conducted with *N*-oxide (200 mg, 1.0 equiv), LiHMDS (1.1 equiv), DMAP, and AC in THF (0.25 M) at r.t. [a] KHMDS was used to replace LiHMDS. [b] 4.74 g of **13** was used.

3. Conclusions

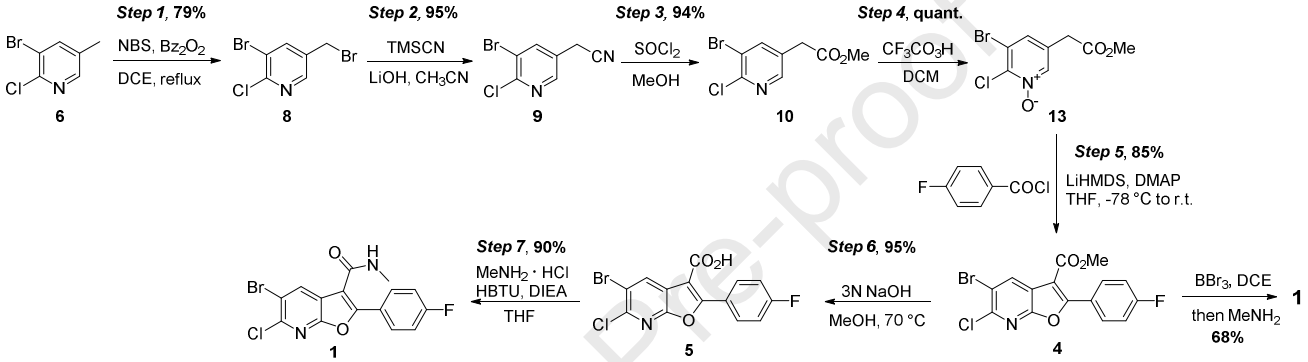
Table 5. Comparison of the key information of synthetic routes

Key information	Route 1	Route 2
Total yield	16%	51% (41%)[a]
Total steps	6	7 (6)[a]
Production scales	**1**: 0.567 g	**1**: 4.66 g
Commercial availability of SM	Y	Y
No. of steps using precious metals	2 (4, 6)[b]	0
No. of steps using highly toxic reagents	1 (CO)	0
No. of steps using halogenating reagents	5 (1-5)[b]	2 (1, 3)[b]
No. of high temperature reactions (≥ 100℃)	0	0
No. of low temperature reactions (< 0 ℃)	0	1(5)[b]
No. of high-pressure reactions	1 (6)[b]	0

[a] Those numbers in the parentheses represent the total yield or total steps using ester aminolysis approach. [b] Those numbers in the parentheses represent the step number of the synthesis.

In conclusion, two novel synthetic approaches to a common and key intermediate for a series of potent HCV NS5B polymerase inhibitors, have been accomplished in 7 or 6 linear steps with an overall yield of 51% or 41% (Scheme 6). Almost every step of the synthesis has been optimized, including several important but not fully explored transformations. Although the synthetic steps are not reduced in comparison with the BMS synthesis, the overall yield has been tripled (Table 5). In addition, those harmful and cost-effective synthetic steps of BMS have been decreased, including reactions requiring the use of halogenating reagents, precious metals, high temperature or high-pressure operation (Table 5). Furthermore, a new synthetic method for 3-cyano substituted 7-azabenzofurans utilizing easily accessible pyridine *N*-oxides as substrates has been developed. The high efficiency and scalability of the synthesis reported herein not only offers the practical large-scale production of this series of HCV NS5B polymerase inhibitors that may be proceeded to on market drugs in future, but also provides a new strategy for the divergent synthesis of various tetrasubstituted 7-azabenzofuran derivatives.

Scheme 6. The whole synthetic route of compound **1**.



4. Experimental section

The preparation experiments were performed under air or an argon atmosphere in oven dried glassware. Solvents used as reaction media were distilled immediately before use: THF was distilled from Na/benzophenone ketyl, DCM and DCE were distilled from calcium hydride, DMF was obtained from vacuum distillation. All reagents were purchased at the highest commercial quality and used without further purification. Oil bath was used as the heat source for those reactions that require heating. Reactions were monitored by thin layer chromatography (TLC) using ultra violet light (UV) as the visualizing agent. Nuclear magnetic resonance spectra (NMR) were recorded on Bruker AV-400 instruments and were calibrated using residual undeuterated solvent as an internal reference (^{1}H NMR: $CHC1_3$ 7.26 ppm, ^{13}C NMR: $CHCl_3$ 77.16 ppm). High resolution mass spectra (HRMS) were recorded on a hybrid IT-TOF mass spectrometer (Shimadzu LCMS-IT-TOF, Kyoto, Japan). The following abbreviations were used to indicate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sep = septet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet).

3-Bromo-5-(bromomethyl)-2-chloropyridine (8). To a solution of compound **6** (5.0 g, 24.22 mmol) in DCE (70 mL) was added NBS (4.3 g, 36.32 mmol) and Bz_2O_2 (587 mg, 2.42 mmol). The resulting solution was heated to reflux and stirred for 6 h. The reaction was complete as indicated by TLC. After cooled down to r.t., the reaction was quenched with water (140 ml) and extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was chromatographed gradiently on silica gel with PE/EA (100:1~50:1) to give the product (5.41 g, 79% yield) as a white solid. The synthesis of **8** has been reported in literature utilizing CCl_4 as solvent but resulted in much lower yield.[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.98 (d, *J* = 1.2 Hz, 1H), 4.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 147.8, 142.7, 134.2, 120.4, 27.3.

2-(5-Bromo-6-chloropyridin-3-yl)acetonitrile (9). To suspension of compound **8** (5.41 g, 19.13 mmol) and $LiOH•H_2O$ (963 mg, 22.96 mmol) in anhydrous CH_3CN (76 mL) at 0 °C was added TMSCN (2.28 g, 22.96 mmol) dropwise under argon atmosphere. The reaction mixture was then warmed to r.t. and stirred for 4 h. The reaction was complete as indicated by TLC. Water and ethyl acetate were added to the mixture. After separation of the organic phase, water phase was extracted by ethyl acetate for two more times. The combined organic phases were washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was chromatographed gradiently on silica gel with PE/EA (20:1~5:1) to give the product (4.18 g, 95% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 2.0 Hz, 1H), 7.97 (d, *J* = 2.0 Hz, 1H), 3.77 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 147.0, 141.7, 126.4, 120.9, 116.0, 20.2. HRMS (-ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_7H_3BrClN_2$ 228.9174; Found 228.9167.

Methyl 2-(5-bromo-6-chloropyridin-3-yl)acetate (10). To a solution of compound **9** (4.18 g, 18.18 mmol) in MeOH (15

mL) was added $SOCl_2$ (3.3 ml, 45.45 mmol) dropwise at 0□. The reaction mixture was increased to r.t. and stirred overnight until the reaction was complete as indicated by TLC. The reaction mixture was concentrated in vacuo. Saturated aqueous $NaHCO_3$ and DCM were added to the residue. After separation of the organic phase, water phase was extracted by DCM for two more times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was chromatographed gradiently on silica gel with PE/EA (30:1~10:1) to give the product (4.47 g, 94% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 2.0 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 3.73 (s, 3H), 3.61 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 149.8, 148.5, 143.2, 130.1, 120.2, 52.7, 37.0. HRMS (+ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_8H_8NO_2ClBr$ 263.9421; Found 263.9411.

3-bromo-2-chloro-5-(2-methoxy-2-oxoethyl)pyridine 1-oxide (13). To a stirred solution of compound **10** (4.47 g, 17.00 mmol) and urea hydrogen peroxide (7.53 g, 80.09 mmol) in DCM (78 mL) was added TFAA (15.29 g, 72.70 mmol) dropwise at 0 °C. The reaction mixture was warmed to r.t and stirred for 1 h. The reaction was complete as indicated by TLC. The excess peroxide was destroyed by saturated aqueous $Na_2S_2O_3$ and water. The resulting mixture was extracted with EA for two times. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the product (4.74 g, 100% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.45 (s, 1H), 3.72 (s, 3H), 3.54 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 142.4, 139.8, 130.9, 130.5, 121.2, 52.8, 37.1. HRMS (+ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_8H_7NO_3ClBrNa$ 301.9190; Found 301.9177.

Methyl 5-bromo-6-chloro-2-(4-fluorophenyl)furo[2,3-b]pyridine-3-carboxylate (4). To a solution of compound **13** (4.74 g, 17.00 mmol) in anhydrous THF (68 mL) under argon was added dropwise a solution of LiHMDS (18.7 mL, 1 M in THF, 18.7 mmol) at -78°C. After the addition, the resulting solution was stirred for 2 h at -78□. 4-Fluorobenzoyl chloride (16.17 g, 101.98 mmol) and DMAP (2.08 g, 16.99 mmol) were then added. The resulting solution was slowly increased to r.t. and stirred overnight. The reaction was quenched with saturated potassium carbonate solution and extracted twice with ethyl acetate. The combined organic extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was chromatographed gradiently on silica gel with PE/EA (100:1~50:1) to give the product (5.53 g, 85% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.16 (dd, *J* = 5.2, 8.8 Hz, 2H), 7.20 (t, *J* = 8.8 Hz, 2H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7 (d, *J* = 253 Hz), 163.0, 160.8, 157.6, 145.8, 137.2, 132.2 (d, *J* = 9 Hz), 124.1 (d, *J* = 3 Hz), 120.2, 116.1, 115.9 (d, *J* = 22 Hz), 107.2, 52.4. HRMS (+ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_9NO_3FClBr$ 383.9433; Found 383.9434.

5-bromo-6-chloro-2-(4-fluorophenyl)furo[2,3-b]pyridine-3-carboxylic acid (5). To a solution of compound **4** (5.53 g, 14.43 mmol) in MeOH (72 mL) was added aqueous NaOH (14.4 ml, 3 N, 43.29 mmol). The resulting mixture was stirred at 70□ for 2 h, cooled to r.t. and acidified with 6 N HCl to pH = 4 ~ 5. Subsequently, the suspension was filtered and the solid was washed with cold water and dried in vacuo to give the product (5.09 g, 95% yield) as a white solid. ^{1}H NMR (400 MHz, d6-DMSO) δ 13.71 (s, 1H), 8.59 (s, 1H), 8.16 (dd, *J* = 5.6, 8.8 Hz, 2H), 7.43 (t, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, d6-DMSO) δ 163.7 (d, *J* = 168 Hz), 163.2, 159.4, 157.1, 143.9, 136.9, 132.3 (d, *J* = 9 Hz), 124.2, 120.9, 115.7 (d, *J* = 22 Hz), 115.1, 108.3. HRMS (-ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{14}H_5BrClFNO_3$ 367.9131; Found 367.9133.

5-bromo-6-chloro-2-(4-fluorophenyl)-N-methylfuro[2,3-b]pyridine-3-carboxamide (1). HBTU (7.61 g, 20.01 mmol) was added to a stirring solution of compound **5** (5.09 g, 13.74 mmol), methylamine hydrochloride (4.57 g, 67.75 mmol) and DIEA (8.76 g, 67.75 mmol) in THF (90 mL). The resulting solution was stirred at r.t. overnight. TLC indicated complete conversion. The solution was then diluted with EtOAc and 1 M HCl. The layers were separated and water layer was extracted with EtOAc. The combined organic extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was chromatographed gradiently on silica gel with PE/EA (50:1~10:1) to afford the desired product (4.66 g, 90% yield) as a white solid. The spectroscopic data are consistent with data previously reported.[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.85 - 7.89 (m, 2H), 7.21 (t, *J* = 8.8 Hz, 2H), 5.89 (s, 1H), 2.98 (d, *J* = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (d, *J* = 252 Hz), 162.8, 157.9, 154.8, 145.7 135.9, 130.9 (d, *J* = 9 Hz), 124.2 (d, *J* = 3 Hz), 120.8, 116.7 (d, *J* = 22 Hz), 115.8, 111.2, 26.7.

Synthesis of compound 1 from compound 4. To a solution of compound **4** (200 mg, 0.52 mmol) in DCE (6.3 mL) was added a solution of BBr_3 (1.15 ml, 1.57 mmol) in DCM (1.57 ml) at 0□ under argon atmosphere. The reaction mixture was increased to r.t. and kept stirring for 4 h. The reaction was then quenched with $MeNH_2$ (10.5 ml, 2 M in THF, 20.88 mmol) and diluted with EtOAc and water. After separation of the two phases, the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude product, which was chromatographed gradiently on silica gel with PE/EA (50:1~10:1) to afford the desired product (135 mg, 68% yield) as a white solid.

3-bromo-2-chloro-5-(cyanomethyl)pyridine 1-oxide (11). To a stirred solution of compound **9** (4.12 g, 17.80 mmol) and urea hydrogen peroxide (6.94 g, 73.79 mmol) in DCM (72 mL) was added TFAA (14.07 g, 66.98 mmol) dropwise at 0 °C. The reaction mixture was warmed to r.t and stirred for 1 h. The reaction was complete as indicated by TLC. The excess peroxide was destroyed by saturated aqueous $Na_2S_2O_3$ and water. The resulting mixture was extracted with EA for two times. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the product (4.40 g, 100% yield) as a white solid. ^{1}H NMR (400 MHz, d6-DMSO) δ 8.53 (t, *J* = 0.8 Hz, 1H), 7.80 (d, *J* = 1.6 Hz, 1H), 4.05 (s, 2H). ^{13}C NMR (100 MHz, d6-DMSO) δ 141.2, 139.1, 129.4, 129.2, 120.7, 117.6, 19.3. HRMS (+ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_7H_4N_2OClBrNa$ 268.9088; Found 268.9076.

5-bromo-6-chloro-2-(4-fluorophenyl)furo[2,3-b]pyridine-3-carbonitrile (12). To a solution of compound **11** (4.40 g, 17.91 mmol) in anhydrous THF (143 mL) under argon was added dropwise a solution of LiHMDS (39.4 mL, 1 M in THF, 39.4 mmol) at -78°C. After the addition, the resulting solution was stirred for 2 h at -78□. 4-Fluorobenzoyl chloride (17.04 g, 107.45 mmol) and DMAP (2.19 g, 17.91 mmol) were then added. The resulting solution was slowly increased to r.t. and stirred overnight. The reaction was quenched with saturated potassium carbonate solution and extracted twice with ethyl acetate. The combined organic extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was chromatographed gradiently on silica gel with PE/EA (100:1~50:1) to give the product (3.70 g, 59% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.12-8.16 (m, 2H), 7.20 (t, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (d, *J* = 255 Hz), 162.0, 157.3, 147.2, 134.2, 129.6 (d, *J* = 9 Hz), 122.9 (d, *J* = 3 Hz), 120.1, 117.3, 117.0 (d, *J* = 8 Hz), 112.6, 86.1. HRMS (+ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_6N_2OFClBr$ 350.9331; Found 350.9341.

Supplenmentary Data

Supplementary data (Supplementary data associated with this article, including NMR spectra) associated with this article can be found in the online version at http://dx.doi.org/10.1016/xxx.

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■ References and notes

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Highlights

- Two practical synthetic approaches to a common and key intermediate for BMT-052.
- 7 steps, total yield: 51%; average yield: 91% per step.
- Harmful or cost-effective synthetic steps have been reduced.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

All authors are inventors on patent application CN202010012690.8, submitted by Tianjin University of Science and Technology, that covers part of the synthetic procedure for the key intermediate of BMT-052. All authors declare no other competing financial interests.