Research Paper

Journal of Chemical Research

Journal of Chemical Research
1–6

DOI: 10.1177/1747519820911271
journals.sagepub.com/home/chl
SAGE

Synthesis of 2-arylamino-5-formyl-pyrimidines from the bis(hexafluorophosphate) Arnold salt

Qiuyu Lu, Wei He, Wen Sun, Ye Feng, Li Zhan and Yu Luo

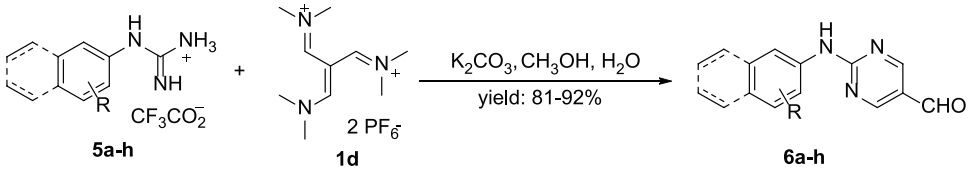
Abstract

A three-step synthesis of 2-arylamino-5-formyl-pyrimidines is developed by condensation of the bis(hexafluorophosphate) Arnold salt with *N*-arylguanidines. This method conveniently provides the corresponding 2-arylaminopyrimidine derivatives in good yields.

Keywords

annulation, Arnold salt, guanidines, pyrimidines, triformylmethane

Date received: 31 December 2019; accepted: 14 February 2020



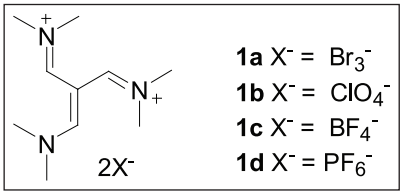


Figure 1. Some typical Arnold salts.

Introduction

The Arnold salt is the only practical source of triformylmethane known to date, which was first isolated by Arnold as the perbromide salt **1a** and perchlorate salt **1b** (Figure 1).[1,2] Afterwards, other Arnold salts were prepared and reported, including tetrafluoroborate salt **1c**,[3,4] hexafluorophosphate salt **1d** and mixed chlorine/bromine trihalide salts.[5,6] These dimethylaminomethylene vinamidinium salts can serve as important three-carbon building blocks for preparing a wide array of carbocycles and heterocycles.[7] 2-Arylaminopyrimidines are found in many biologically active natural products and also serve as components of a number of prominent commercial drugs, such as imatinib, nilotinib, pazopanib and rilpivirine (Figure 2).[8–11] Not surprisingly, the synthesis of these building blocks is an attractive subject in organic chemistry. Although the previously published approach to access 2,5-disubstituted pyrimidines involved the condensation of Arnold salts with appropriate nucleophiles, the most widely used Arnold salt was the perchlorate salt **1b**,[12] a high-energy material with significant shock sensitivity.[13] Although the tetrafluoroborate salt **1c**, a safer Arnold salt, was used by Ragan to prepare a variety of 2,5-disubstituted pyrimidines,[14] it was hygroscopic and thus not very convenient to handle. Moreover, in the published synthesis of 2,5-disubstituted pyrimidines, the nucleophiles were mainly amidines and a few *N*-alkylguanidines,[15] while the condensation of Arnold salts with *N*-aryl-guanidines to afford 2-arylaminopyrimidines has scarcely been reported.

Since bis(hexafluorophosphate) Arnold salt **1d** is a safe and non-hygroscopic material with a well-determined molecular weight, this Arnold salt should be an attractive alternative. Curiously, the literature reports about the use of in salt **1d** heterocycle synthesis and its thermal analysis are very scarce.[14,16] To further explore the potential utility of this bis(hexafluorophosphate) Arnold salt **1d**, we investigated its condensation with a series of *N*-arylguanidines. As a result, some interesting pyrimidine derivatives have been synthesized in moderate to good yields. Herein, we report the details of our investigations.

Department of Chemistry, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai, P.R. China

Corresponding author:
Yu Luo, Department of Chemistry, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200241, P.R. China.
Email: yluo@chem.ecnu.edu.cn

Results and discussion

Our synthesis of bis(hexafluorophosphate) salt **1d** was through a slightly modified process, using inexpensive malonic acid as the starting material instead of the irritant bromoacetic acid.[17] After carbon dioxide evolution had ceased, aqueous ammonium hexafluorophosphate was added to the mixture to precipitate the corresponding vinamidinium salt (Scheme 1). As far as we know, the differential scanning calorimetry (DSC) analysis of **1d** has not been reported before. Thus, the DSC analysis of **1d** was first tested and the result showed that its energy was 257 J/g. This result confirmed that the hexafluorophosphate salt should be very stable.

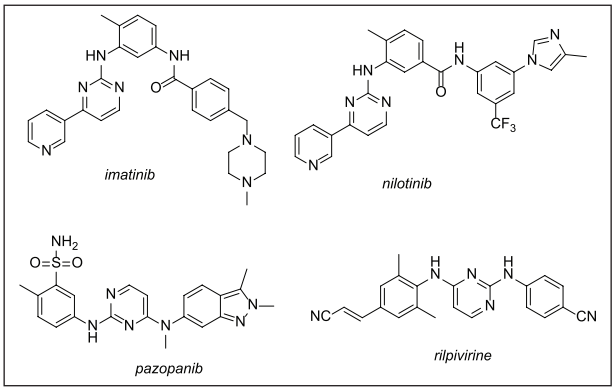
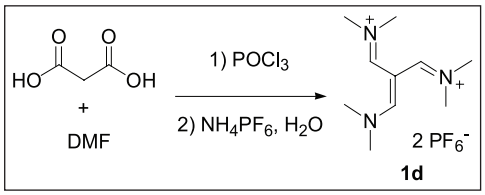


Figure 2. Examples of drugs with 2-arylaminopyrimidine moieties.

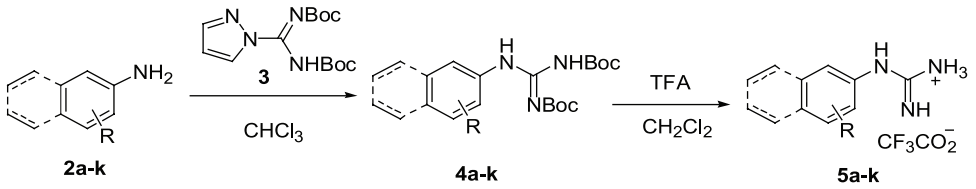


Scheme 1. Our synthesis of **1d**.

With the desired salt in hand, we attempted to prepare an array of *N*-arylguanidines. The direct coupling of aromatic amines with cyanamide under acidic conditions is a straightforward method to prepare *N*-arylguanidines. However, this protocol was not appealing since the resulting crude products were difficult to purify and the yields were fairly low with significant qualities of aromatic amines recovered. Thus, a two-step method was adopted. Aromatic amines **2a**–**k** were first treated with *N,N′-bis*-Boc-1*H*-pyrazole-1-carboxamidine (**3**) to give *bis*-Boc guanidines **4a**–**h**, which were deprotected under acidic conditions to afford the desired products **5a**–**h** (Table 1). Generally, the yields of the *bis*-Boc guanidines were good. However, the reactions with 2-chloro-6-methyl-phenylamine (**2i**), 4-nitro-aniline (**2j**) and 4-trifluoromethylphenylamine (**2k**) failed to give the desired products (Table 1, entries 9–11), with only the starting materials being recovered. This suggested that steric and electronic effects played crucial roles in this substitution reaction. Both steric hindrance and the presence of electron-withdrawing groups dramatically reduced the nucleophilicity of these anilines.

Subsequently, the condensation of Arnold salt **1d** with guanidine **5a** was used to screen for the reaction conditions (Table 2). Among the three bases screened, potassium carbonate gave an excellent yield (Table 2, entry 3). Sodium carbonate was also good, but the reaction time was longer (Table 2, entry 4). Sodium bicarbonate, a weaker base, also afforded the product in a good yield (Table 2, entry 5). However, if no base was added, the reaction did not occur

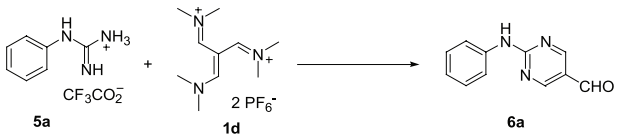
Table 1. The structures and yields of compounds **4** and **5**.[a]



Entry	R	Product **4**	Yield (%)[b]	Product **5**	Yield (%)[b]
1	H	**4a**	84	**5a**	85
2	4-F	**4b**	87	**5b**	80
3	4-CH_3	**4c**	85	**5c**	68
4	2-CH_3, 4-Br	**4d**	68	**5d**	68
5	3-Cl	**4e**	78	**5e**	65
6	4-Cl	**4f**	87	**5f**	87
7	4-CH_3O	**4g**	89	**5g**	85
8	H (2-naphthylamine)	**4h**	85	**5h**	83
9	2-Cl-6-CH_3	**4i**	–	**5i**	NA
10	4-NO_2	**4j**	–	**5j**	NA
11	4-CF_3	**4k**	–	**5k**	NA

TFA: trifluoroacetic acid; –: no product obtained; NA: not available.
[a]Reagents and conditions: a mixture of **2a–k** and **3** in chloroform was refluxed for 5 h (for the first step); a mixture of **4a–h** in TFA and dichloromethane was stirred at room temperature for 4 h (for the second step).
[b]Isolated yield.

Table 2. Effect of bases and solvents on the condensation.[a]

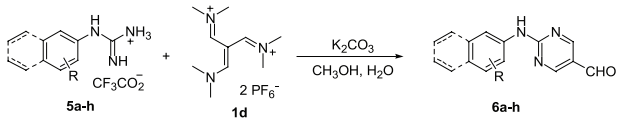


5a 1d 6a

Entry	Base	Solvent	Time (h)	Yield (%)[b]
1	None	CH_3OH/H_2O[c]	3	–
2	K_2CO_3	CH_3OH	5	–
3	K_2CO_3	CH_3OH/H_2O[c]	3	92
4	Na_2CO_3	CH_3OH/H_2O[c]	5	90
5	$NaHCO_3$	CH_3OH/H_2O[c]	6	80
6	K_2CO_3	CH_3OH	5	85
7	K_2CO_3	DMF	5	81

DMF: dimethylformamide; –: no product obtained.
[a]Reagents and conditions: a mixture of **5a**, **1d** and the base (except for entry 1) in solvent was stirred at 50°C.
[b]Isolated yield.
[c]Methanol:water = 3:1.

Table 3. Synthesis of 2-arylamino-5-formyl-pyrimidines.[a]



5a-h 1d 6a-h

Entry	R	Time (h)	Product	Yield (%)[b]
1	H	6	**6a**	92
2	4-F	5	**6b**	87
3	4-CH_3	12	**6c**	90
4	2-CH_3, 4-Br	12	**6d**	83
5	3-Cl	4.5	**6e**	81
6	4-Cl	7	**6f**	80
7	4-CH_3O	12	**6g**	90
8	H (2-naphthylamine)	12	**6h**	88

[a]Reagents and conditions: a mixture of **5a–h** and **1d** in methanol and water was stirred at 50°C for 6 h.
[b]Isolated yield.

(Table 2, entry 1). The effect of solvents was also explored. It was found that a mixture of methanol and water gave good yields (Table 2, entries 3–5), while pure methanol did not yield the product (Table 2, entry 2). The use of a protic solvent dimethylformamide (DMF) produced **6a**, but the reaction time was much longer and the yield was decreased. With the protocol in hand, the remaining guanidines **5b–h** were condensed with Arnold salt **1d** using potassium carbonate as base in a mixture of methanol and water. The reactions proceeded smoothly, and the yields of the desired products were good to excellent (Table 3).

Conclusion

In conclusion, the condensation of *N*-arylguanidines with bis(hexafluorophosphate) Arnold salt **1d** is a facile method for the synthesis of *N*-arylpyrimidines. This method is convenient and the overall yields were generally good.

Experimental

Commercial reagents were used without further purification. Melting points were measured on a SGW X-4 (INESA) melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker DRX-500 (500 MHz) or DRX-600 (600 MHz) instrument. ^{13}C NMR spectra were obtained on JNMEX400 (125 MHz) or JNMEX400 (150 MHz) instrument. Mass spectra (MS) were recorded on a Bruker MicrOTOF II mass spectrometer or a Waters High Resolution UPLCTOFMS spectrometer. Infrared (IR) spectra were obtained using attenuated total reflectance (ATR) on a Fourier transform infrared (FTIR) Bruker Tensor 27. DSC was determined on a Mettler Toledo TGA/DSC 3+.

General procedure for the synthesis of Arnold salt 1d

*Synthesis of bis(hexafluorophosphate) Arnold salt (**1d**).* Trichlorophosphate (73 g, 0.48 mol) was added dropwise to DMF (63.3 g, 0.87 mol) at 0°C. Next, malonic acid (15 g, 0.14 mol) was added and the resulting mixture was stirred at 90°C for 7 h. NH_4PF_6 (47 g, 0.29 mol) was dissolved in ice water and added to the reaction mixture. The Arnold salt precipitated and was triturated with isopropanol (120 mL) to give pure **1d** as a light yellow solid: Yield 43.7 g (64%); m.p. 200–203°C; ^{1}H NMR (CD_3CN, 500 MHz): δ = 8.01 (s, 3H), 3.52 (s, 9H), 3.38 (s, 9H); ^{13}C NMR (CD_3CN, 125 MHz): δ = 164.4, 90.8, 49.1, 43.2.

General procedure for the synthesis of bis-*Boc guanidines*

*Synthesis of 1-[2,3-di(tert-butoxycarbonyl)guanidino]-4-benzene (**4a**).* *N,N′-bis*-Boc-1*H*-pyrazole-1-carboxamidine (**3**) (1.0 g, 3.22 mol) and aniline **2a** (0.39 g, 4.23 mmol) were dissolved in $CHCl_3$ (5 mL). The resulting mixture was stirred for 5 h at 50°C. The organic phase was washed with 1 M HCl solution (5 mL), dried and evaporated to give the crude product. The residue was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **4a** as a colourless solid[18]: Yield 0.91 g (84%); m.p. 128–130°C (lit. 129–132°C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.67 (s, 1H), 10.36 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.9 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 1.56 (s, 9H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 153.5, 153.3, 136.7, 128.8, 124.7, 122.1, 83.7, 79.7, 28.1. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{26}N_3O_4$: 336.1918; found: 336.1917.

*Synthesis of 1-[2,3-di(tert-butoxycarbonyl)guanidino]-4-fluorobenzene (**4b**).* The general procedure was followed (3.22 mmol scale). The crude residue was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **4b** as a colourless solid: Yield 0.99 g (87%); m.p. 135–137°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.65 (s, 1H), 10.31 (s, 1H), 7.56–7.59 (m, 2H), 7.04 (t, *J* = 8.6 Hz, 2H), 1.56 (s, 9H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 153.4, 153.3, 138.0, 134.4, 129.8, 124.7, 121.1 (d, *J* = 241.3 Hz), 84.0, 79.9, 28.1, 28.0; HRMS (ESI) *m/z*

$[M+H]^+$ calcd for $C_{17}H_{25}FN_3O_4$: 354.1824; found: 354.1818; IR: 2998, 1716, 1494, 1305 cm^{-1}.

*Synthesis of 1-[2,3-di(tert-butoxycarbonyl)guanidino]-4-methylbenzene (**4c**).* The general procedure was followed (3.22 mmol scale). The crude residue was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **4c** as a colourless solid[19]: Yield 0.96 g (85%); m.p. 120–122°C (lit. 120–122°C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.68 (s, 1H), 10.28 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 2.33 (s, 3H), 1.56 (s, 9H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.4, 153.5, 153.3, 134.4, 134.1, 129.3, 122.2, 83.6, 79.5, 28.2, 28.1, 20.9; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{28}N_3O_4$: 350.2074; found: 350.2070.

*Synthesis of 1-[2,3-di(tert-butoxycarbonyl)guanidino]-2-methyl-4-bromobenzene (**4d**).* The general procedure was followed (3.22 mmol scale). The crude residue was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **4d** as a colourless solid: Yield 0.94 g (68%); m.p. 161–164°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.69 (s, 1H), 10.19 (s, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.28–7.36 (m, 2H), 2.30 (s, 3H), 1.56 (s, 9H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 153.7, 153.4, 134.3, 132.9, 132.1, 129.5, 125.7, 118.0, 83.8, 79.8, 28.1, 28.0, 17.9; HRMS (ESI) *m/z* $[M\ (^{79}Br)]^+$ calcd for $C_{18}H_{27}BrN_3O_4$: 428.1179; $[M\ (^{81}Br)]^+$: 430.1159; found: 428.1173; 430.1154; IR: 2983, 1708, 1487, 1305 cm^{-1}.

*Synthesis of 1-[2,3-di(tert-butoxycarbonyl)guanidino]-3-chlorobenzene (**4e**).* The general procedure was followed (3.22 mmol scale). The crude residue was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **4e** as a colourless solid: Yield 0.93 g (78%); m.p. 145–148°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.64 (s, 1H), 10.41 (s, 1H), 7.70 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.13–7.08 (m, 1H), 1.56 (s, 9H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 160.7, 158.8, 153.6, 153.3, 132.7, 124.0, 123.9, 115.6, 115.4, 83.8, 79.7, 28.1, 28.0; HRMS (ESI) *m/z* $[M\ (^{35}Cl)+H]^+$ calcd for $C_{17}H_{25}ClN_3O_4$: 370.1528; $[M\ (^{37}Cl)+H]^+$: 372.1499; found: 370.1522; 372.1498; IR: 2893, 1708, 1487, 1297, 759 cm^{-1}.

*Synthesis of 1-[2,3-di(tert-butoxycarbonyl)guanidino]-4-chlorobenzene (**4f**).* The general procedure was followed (3.22 mmol scale). The crude residue was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **4f** as a colourless solid[20]: Yield 1.04 g (87%); m.p. 141–144°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.64 (s, 1H), 10.37 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.3–7.29 (m, 2H), 1.56 (s, 9H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 153.4, 153.3, 135.4, 129.8, 128.9, 123.3, 83.9, 79.9, 28.1, 28.0; HRMS (ESI) *m/z* $[M\ (^{35}Cl)+H]^+$ calcd for $C_{17}H_{25}ClN_3O_4$: 370.1528; $[M\ (^{37}Cl)+H]^+$: 372.1499; found: 370.1534; 372.1507.

*Synthesis of 1-[2,3-di(tert-butoxycarbonyl)guanidino]-4-methoxybenzene (**4g**).* The general procedure was followed (3.22 mmol scale). The crude residue was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **4g** as a colourless solid: Yield 1.05 g (89%); m.p. 115–116°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.66 (s, 1H), 10.20 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H), 1.55 (s, 9H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.6, 156.8, 153.6, 153.3, 129.8, 123.8, 114.0, 83.5, 79.4, 55.4, 28.2, 28.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{28}N_3O_5$: 366.2023; found: 366.2033; IR: 2982, 1726, 1507, 1297, 764 cm^{-1}.

*Synthesis of 1-[2,3-di(tert-butoxycarbonyl)guanidino]-naphthalene (**4h**).* The general procedure was followed (3.22 mmol scale). The crude residue was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **4h** as a colourless solid: Yield 1.06 g (85%); m.p. 146–148°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.72 (s, 1H), 10.55 (s, 1H), 8.20 (s, 1H), 7.79–7.84 (m, 3H), 7.67–7.70 (m, 1H), 7.50–7.40 (m, 2H), 1.58 (s, 9H), 1.55 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.6, 153.6, 153.4, 134.3, 133.7, 130.9, 128.5, 127.8, 127.5, 126.2, 125.1, 121.9, 119.2, 83.8, 79.7, 28.2, 28.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{28}N_3O_4$: 386.2074; found: 386.2081; IR: 2972, 1716, 1507, 1371 cm^{-1}.

General procedure for the synthesis of guanidines

Synthesis of 1-phenylguanidine trifluoroacetate **(5a).** 1-[2,3-Di(tert-butoxycarbonyl)guanidino]-4-benzene **(4a)** (0.95 g, 2.83 mmol) was dissolved in CF_3COOH (3 mL) and $CHCl_3$ (3 mL). The resulting mixture was stirred for 5 h at 50°C and then evaporated to dryness. The crude residue was triturated with 50% ethyl acetate in petroleum ether (3 mL) to give **5a** as a colourless solid[21]: Yield 0.6 g (85%); m.p. 160–163°C (lit. 175–177°C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 10.25 (s, 1H), 7.73 (s, 4H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.34–7.18 (m, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 160.3 (q, *J* = 32.4 Hz), 156.4, 135.9, 130.1, 126.7, 124.7, 117.3 (q, *J* = 297.2 Hz); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_7H_{10}N_3$: 136.0869; found: 136.0868.

Synthesis of 1-(4-fluorophenyl)guanidine trifluoroacetate **(5b).** The general procedure was followed (2.83 mmol scale). The crude residue was triturated with 50% ethyl acetate in petroleum ether (3 mL) to give **5b** as a colourless solid: Yield 0.6 g (80%); m.p. 145–148°C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 10.11 (s, 1H), 7.66 (s, 4H), 7.29 (d, *J* = 8.1 Hz, 4H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 160.9 (d, *J* = 241.9 Hz), 160.1 (q, *J* = 32.0 Hz), 156.8, 132.0, 127.9 (d, *J* = 8.8 Hz), 117.4 (q, *J* = 296.0 Hz) 116.8 (d, *J* = 22.6 Hz); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_7H_9FN_3$: 154.0755; found: 154.0785; IR: 3165, 1502, 1436, 1178 cm^{-1}.

*Synthesis of 1-(p-tolyl)guanidine trifluoroacetate (**5c**).* The general procedure was followed (2.83 mmol scale). The crude residue was triturated with 50% ethyl acetate in petroleum ether (3 mL) to give **5c** as a colourless solid: Yield 0.51 g (68%); m.p. 77–80°C; ^{1}H NMR (DMSO-d_6,

500 MHz): δ = 10.11 (s, 1H), 7.63 (s, 4H), 7.13–7.26 (m, 4H), 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 160.0 (q, J = 32.4 Hz), 156.6, 136.3, 133.1, 130.5, 125.1, 117.3 (q, J = 297.3 Hz), 20.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_8H_{12}N_3$: 150.1026; found: 150.1028.

Synthesis of 1-(4-bromo-2-methylphenyl)guanidine trifluoroacetate **(5d)**. The general procedure was followed (2.83 mmol scale). The crude residue was triturated with 50% ethyl acetate in petroleum ether (3 mL) to give **5d** as a colourless solid: Yield 0.66 g (68%); m.p. 145–148°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 9.89 (s, 1H), 7.46–7.61 (m, 6H), 7.18 (d, J = 8.3 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 160.2 (q, J = 32.1 Hz), 156.9, 138.5, 134.0, 133.4, 130.4, 130.2, 121.0, 117.3 (q, J = 297.1 Hz), 17.4; HRMS (ESI) m/z $[M\ (^{79}Br) + H]^+$ calcd for $C_8H_{11}BrN_3$: 228.0131; $[M\ (^{81}Br) + H]^+$: 230.0110; found: 228.0135; 230.0118; IR: 3141, 1494, 1265, 1130, 719 cm^{-1}.

Synthesis of 1-(3-chlorophenyl)guanidine trifluoroacetate **(5e)**. The general procedure was followed (2.83 mmol scale). The crude residue was triturated with 50% ethyl acetate in petroleum ether (3 mL) to give **5e** as a colourless solid: Yield 0.52 g (65%); m.p. 134–137°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 10.39 (s, 1H), 7.87 (s, 4H), 7.57–7.09 (m, 4H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 160.4 (q, J = 32.5 Hz), 156.41, 137.7, 134.1, 131.6, 126.4, 124.5, 123.3, 117.3 (q, J = 296.9 Hz); HRMS (ESI) m/z $[M\ (^{35}Cl) + H]^+$ calcd for $C_7H_9ClN_3$: 170.0480; $[M\ (^{37}Cl) + H]^+$: 172.0450; found: 170.0487; 172.0455; IR: 3466, 3133, 1487, 1265 cm^{-1}.

Synthesis of 1-(4-chlorophenyl)guanidine trifluoroacetate **(5f)**. The general procedure was followed (2.83 mmol scale). The crude residue was triturated with 50% ethyl acetate in petroleum ether (3 mL) to give **5f** as a colourless solid[21]: Yield 0.7 g (87%); m.p. 124–127°C (lit. 139–141°C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 10.35 (s, 1H), 7.82 (s, 4H), 7.27–7.50 (m, 4H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 160.5 (q, J = 33.1 Hz), 156.5, 135.0, 130.9, 130.0, 126.7, 117.3 (q, J = 296.7 Hz); HRMS (ESI) m/z $[M\ (^{35}Cl) + H]^+$ calcd for $C_7H_9ClN_3$: 170.0480; $[M\ (^{37}Cl) + H]^+$: 172.0450; found: 170.0498; 172.0468.

*Synthesis of 1-(4-methoxyphenyl)guanidine trifluoroacetate (***5g***)*. The general procedure was followed (2.83 mmol scale). The crude residue was triturated with 50% ethyl acetate in petroleum ether (3 mL) to give **5g** as a colourless solid: Yield 0.67 g (85%); m.p. 124–127°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 9.87 (s, 1H), 7.50 (s, 4H), 7.00–7.19 (m, 4H), 3.77 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 159.9 (q, J = 31.9 Hz), 158.4, 156.9, 128.1, 127.5, 117.4 (q, J = 297.5 Hz), 115.2, 55.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_8H_{12}N_3O$: 166.0975; found: 166.0984; IR: 3153, 1497, 1278, 1126, 717.

*Synthesis of 1-(naphthalen-2-yl)guanidine trifluoroacetate (***5h***)*. The general procedure was followed (2.83 mmol scale). The crude residue was triturated with 50% ethyl acetate in petroleum ether (3 mL) to give **5h** as a colourless solid: Yield 0.7 g (83%); m.p. 137–140°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 10.36 (s, 1H), 8.05–7.90 (m, 3H), 7.79 (d, J = 8.1 Hz, 5H), 7.63–7.47 (m, 2H), 7.38–7.40 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 160.03 (q, J = 31.9 Hz), 156.6, 133.7, 133.4, 131.7, 129.9, 128.1, 128.0, 127.1, 126.5, 123.8, 122.6, 117.4 (q, J = 297.7 Hz); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_{12}N_3$: 186.1026; found: 186.1038; IR: 3172, 1507, 1250, 1126, 717 cm^{-1}.

General procedure for the synthesis of N-*arylpyrimidines*

*Synthesis of 2-(phenylamino)pyrimidine-5-carbaldehyde (***6a***)*. 1-Phenylguanidine trifluoroacetate (**5a**) (0.92 g, 3.7 mmol), bis(hexafluorophosphate) Arnold salt (**1d**) (1.75 g, 3.7 mmol) and K_2CO_3 (1.02 g, 7.4 mmol) were dissolved in methanol (20 mL) and water (7 mL). The mixture was stirred at 50°C for 6 h. The solvent was removed in vacuum and the aqueous layer was extracted with ethyl acetate (15 mL). The combined organic layer was dried over Na_2SO_4, filtered and the solvent removed in vacuum. The crude residue was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **6a** as a light yellow solid[22]: Yield 0.68 g (92%); m.p. 183–184°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.90 (s, 1H), 8.88 (s, 2H), 8.06 (s, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 187.5, 161.7, 160.6, 137.6, 129.1, 124.6, 122.1, 120.7; LRMS: (ESI): m/z (%): 200 (100) $[M + 1]^+$.

*Synthesis of 2-[(4-fluorophenyl)amino]pyrimidine-5-carbaldehyde (***6b***)*. The general procedure was followed (3.7 mmol scale). The crude residue was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **6b** as a light yellow solid: Yield 0.70 g (87%); m.p. 213–215°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 10.50 (s, 1H), 9.84 (s, 1H), 8.90 (s, 2H), 7.76–7.79 (m, 2H), 7.19 (t, J = 8.7 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 189.3, 161.7, 160.9, 158.6 (d, J = 240.2 Hz), 135.7, 122.7 (d, J = 7.9 Hz), 122.0, 115.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_9FN_3O$: 218.0724; found: 218.0731; IR: 3260, 1684, 1510, 1352 cm^{-1}.

*Synthesis of 2-(p-tolylamino)pyrimidine-5-carbaldehyde (***6c***)*. The general procedure was followed (3.7 mmol scale). The crude residue was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **6c** as a light yellow solid: Yield 0.71 g (90%); m.p. 168–170°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 10.39 (s, 1H), 9.82 (s, 1H), 8.88 (s, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 189.2, 161.8, 160.9, 136.7, 132.8, 129.4, 121.7, 120.9, 20.9; LRMS (ESI): m/z (%): 214 (100) $[M + 1]^+$.

*Synthesis of 2-[(4-bromo-2-methylphenyl)amino]pyrimidine-5-carbaldehyde (***6d***)*. The general procedure was followed (3.7 mmol scale). The crude residue was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **6d** as a pink solid: Yield 0.90 g (83%); m.p. 189–191°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 9.90 (s,

1H), 9.80 (s, 1H), 8.81 (s, 2H), 7.50 (s, 1H), 7.40 (d, J=7.1 Hz, 1H), 7.34 (d, J=8.5 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=189.2, 162.8, 161.1, 136.7, 136.6, 133.2, 129.3, 128.7, 121.7, 118.4, 18.1; HRMS (ESI): *m/z* [M (^{79}Br) + H]$^+$ calcd for $C_{12}H_{11}BrN_3O$: 292.0080; [M (^{81}Br) + H]$^+$: 294.0060; found: 292.0076; 294.0059; IR: 3244, 1684, 1518, 1360 cm^{-1}.

*Synthesis of 2-[(3-chlorophenyl)amino]pyrimidine-5-carbaldehyde (**6e**).* The general procedure was followed (3.7 mmol scale). The crude residue was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **6e** as a yellow solid: Yield 0.70 g (81%); m.p. 197–200°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ=10.60 (br, 1H), 9.86 (s, 1H), 8.95 (s, 2H), 7.98 (s, 1H), 7.70 (d, J=8.0 Hz, 1H), 7.36 (t, J=8.1 Hz, 1H), 7.10 (d, J=7.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=189.4, 161.6, 160.8, 141.0, 133.4, 130.7, 123.1, 122.4, 119.7, 118.9; HRMS (ESI): *m/z* [M (^{35}Cl) + H]$^+$ calcd for $C_{11}H_9ClN_3O$: 234.0429; [M (^{37}Cl) + H]$^+$: 236.0399; found: 234.0427; 236.0396; IR: 3260, 3217, 1661, 1510, 766 cm^{-1}.

*Synthesis of 2-[(4-chlorophenyl)amino]pyrimidine-5-carbaldehyde (**6f**).* The general procedure was followed (3.7 mmol scale). The crude residue was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **6f** as a light yellow solid: Yield 0.69 g (80%); m.p. 191–194°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ=10.60 (s, 1H), 9.86 (s, 1H), 8.93 (s, 2H), 7.82 (d, J=8.7 Hz, 2H), 7.40 (d, J=8.7 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=189.4, 161.6, 160.9, 138.4, 128.9, 127.2, 122.2, 122.1; LRMS (ESI): *m/z* (%): 234 (100) [M (^{35}Cl) + 1]$^+$, 236 (35) [M (^{37}Cl) + 1]$^+$.

*Synthesis of 2-[(4-methoxyphenyl)amino]pyrimidine-5-carbaldehyde (**6g**).* The general procedure was followed (3.7 mmol scale). The crude residue was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **6g** as a yellow solid: Yield 0.76 g (90%); m.p. 145–146°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=9.87 (s, 1H), 8.83 (s, 2H), 7.53 (d, J=8.9 Hz, 2H), 7.28 (s, 1H), 6.96 (d, J=8.9 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=187.5, 162.0, 156.9, 130.4, 123.2, 121.8, 114.3, 55.5; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{11}N_3NaO_2$: 252.0743; found: 252.0472; IR: 3276, 1669, 1507, 1365 cm^{-1}.

*Synthesis of 2-(naphthalen-2-ylamino)pyrimidine-5-carbaldehyde (**6h**).* The general procedure was followed (3.7 mmol scale). The crude residue was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **6h** as a light yellow solid: Yield 0.81 g (88%); m.p. 186–189°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ=10.71 (s, 1H), 9.88 (s, 1H), 8.98 (s, 2H), 8.44 (s, 1H), 7.42–7.89 (m, 6H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ=189.3, 161.9, 160.9, 137.0, 133.8, 130.1, 128.6, 127.9, 127.7, 126.9, 125.1, 122.1, 121.5, 116.5; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{12}N_3O$: 250.0975; found: 250.0976; IR: 3267, 1669, 1516, 1374 cm^{-1}.

Acknowledgements

The authors thank the Laboratory of Organic Functional Molecules and the Sino-French Institute of ECNU for their support.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

ORCID iD

Yu Luo https://orcid.org/0000-0002-9570-796X

Supplemental material

Supplemental material for this article is available online.

References

1. Aronld Z. *Coll Czech Chem Commun* 1961; 26: 3051.
2. Aronld Z. *Coll Czech Chem Commun* 1965; 30: 2125.
3. Keshavarz KM, Cox SD, Angus JRO, et al. *Synthesis* 1988; 641.
4. Jameleddine K, Adnen HAM and Bechir BH. *Tetrahedron Lett* 2006; 47: 2973.
5. Davies IW, Tellers DM, Shultz CS, et al. *Org Lett* 2002; 4: 2969.
6. Sawai Y, Mizuno M, Ito T, et al. *Tetrahedron* 2014; 70: 2370.
7. Chtiba S, Jemmezi F and Khiari J. *Tetrahedron Lett* 2011; 52: 3648.
8. Zhang X, Sun JJ, Chen T, et al. *Synlett* 2016; 27: 2233.
9. Ueda S, Su MJ and Buchwald SL. *J Am Chem Soc* 2012; 134: 700.
10. Mei YC, Yang BW, Chen W, et al. *Lett Org Chem* 2012; 9: 276.
11. Guillemont J, Pasquier E, Palandjian P, et al. *J Med Chem* 2005; 48: 2072.
12. Gupton JT, Gall JE, Riesinger SW, et al. *J Heterocycl Chem* 1991; 28: 1281.
13. Ragan JA, am Ende DJ, McHardy SJ, et al. *Chem Eng News* 2000; 78: 8.
14. Ragan JA, McDermott RE, Jones BP, et al. *Synlett* 2000; 8: 1172.
15. Stephen PK, Cameron JC, Bishop BC, et al. *J Org Chem* 2005; 70: 1771.
16. Yamano M, Sawai Y and Mizuno M. Patent EP2258676A1, Japan, 2008.
17. Khiari J, Hadj AMA and Ben HB. *Tetrahedron Lett* 2006; 47: 2973.
18. Ohara K, Vasseur JJ and Smietana M. *Tetrahedron Lett* 2009; 50: 1463.
19. Rodriguez F, Rozas I, Ortega JE, et al. *J Med Chem* 2008; 51: 3304.
20. Magri A, Reilly R, Scalacci N, et al. *Bioorg Med Chem Lett* 2015; 25: 5372.
21. Hammoud H, Schmitt M, Bihe F, et al. *J Org Chem* 2012; 77: 417.
22. AlNeyadi SS, Salem AA, Ghattas MA, et al. *Eur J Med Chem* 2017; 136: 270.