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THE NEW CONVENIENT SYNTHESIS OF 6-FLUOROPURINE AND ITS 7-/9-UNSUBSTITUTED ANALOGUES

Mei Deng, Ningyu Wang, Guangming Xiang, and Luoting Yu*

State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu 610041, China; E-mail: yuluot@scu.edu.cn

Abstract – 6-Fluoropurine and its 7-/9-unsubstituted analogues have good biological activity and serve as important pharmaceutical intermediates. This paper describes a new and convenient synthesis of 6-fluoropurine and its 7-/9-unsubstituted analogues, by first replacing the chlorine atoms with trimethylammonio groups through the reaction of 6-chloropurine and its 7-/9-unsubstituted analogues with trimethylamine, and then replacing the trimethylammonio groups with fluorine atoms using safe and cheap TBAF·3H_2O as fluorinating agent at room temperature. Compared with reported methods, the new synthesis has milder conditions, shorter reaction times, simpler post-processing and higher (or similar) yields.

6-Fluoropurine and its 7-/9-unsubstituted analogues have good biological activity and serve as important pharmaceutical intermediates.[1,2] Purines are integral parts of DNA and RNA. Purine analogues are a very important class of nucleoside pharmaceutical intermediates and have special effect on cancer, AIDS, leukemia and others.[3-9] Fluorine-substituted compounds such as Fludarabine, show remarkable differences in biological activities and pharmacological properties compared to their parent molecules, as introduction of fluorine can improve the metabolic stability, modulate the physicochemical properties and increase binding affinity to a target protein.[10,11]

According to the literature,[12-16] 6-fluoropurine and its 7-/9-unsubstituted analogues can be obtained by the following methods: (i) 6-chloropurine and its 7-/9-unsubstituted analogues react with dry potassium

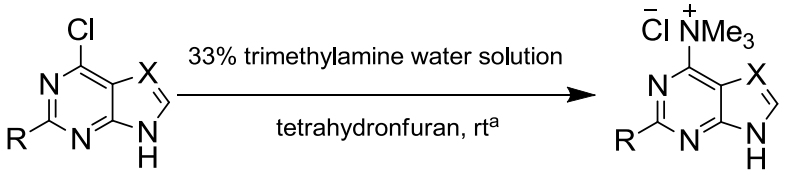
fluoride in dry DMSO at 180 ˚C using tetraphenylphosphonium bromide as phase transfer catalyst; (ii) 6-chloropurine and its 7-/9-unsubstituted analogues react with dry potassium fluoride under microwave using ionic liquid as solvent; (iii) a modified Schiemann Reaction on an aminopurine in which the diazotization product is treated with fluoroboric acid; (iv) displacement of trimethylammonio groups formed by the reaction of 6-chloropurine and its 7-/9-unsubstituted analogues with trimethylamine, on treatment with hydrogen potassium fluoride; (v) fluorination of 6-chloropurine and its 7-/9-unsubstituted analogues using "anhydrous" tetrabutylammonium fluoride ($TBAF_{anh}$) in anhydrous DMSO at 20 ˚C.

But all the five methods have disadvantages: methods (i) and (ii) need high temperatures, and ionic liquid used in method (ii) is hard to get; method (iii) gives low yields and needs harsh reaction conditions; method (iv) uses hydrogen potassium fluoride which is corrosive, giving poor yields of products (6-fluoropurine, 35% and 2-chloro-6-fluoropurine, 32%) and considerable amounts of byproducts, and sometimes the reaction should be heated (6-fluoropurine, 60 ˚C); method (v) requires long reaction times (6-fluoropurine, 14 days) ending up with low yields (6-fluoropurine, 65%), and high vacuum (<0.1 mmHg) demanded in the preparation of $TBAF_{anh}$ is difficulty to achieve.

In order to find a new convenient synthesis of 6-fluoropurine and its 7-/9-unsubstituted analogues, we first analyzed the causes leading to the long reaction times and low yields in method (v) which has the mildest reaction conditions in the five methods. It was found that $TBAF_{anh}$ behaves not only as a good source of nucleophilic fluoride but also a strong base and hydrolyzing agent,[17] and it deprotonates 6-fluoropurine and its 7- or 9-unsubstituted analogues, generating an equivalent of bifluoride ion[16] and resulting in some degree of deactivation of the reactants.

It was reported that safe, commercially available and cheap trihydrate tetrabutylammonium fluoride ($TBAF{\cdot}3H_2O$) is a powerful, nonbasic and nucleophilic fluorinating agent,[17] but it could not fluorinate 6-chloropurine and its 7-/9-unsubstituted analogues (**1a-1c)**, because of its weaker nucleophilicity of fluoride ion than that in $TBAF_{anh}$. To solve the problem, we first replaced the chlorine atoms with trimethylammonio groups which are better leaving groups, through the reaction of 6-chloropurine and its 7-/9-unsubstituted analogues (**1a-1c)** with aqueous solution of trimethylamine[15,18] in high yields (see Table 1), and then replaced the trimethylammonio groups with fluorine atoms using $TBAF{\cdot}3H_2O$ as fluorinating agent (see Table 2).

Table 1. Replacement of the chlorine atoms in 6-chloropurine and its 7-/9-unsubstituted analogues (**1a-1c)** with trimethylammonio groups



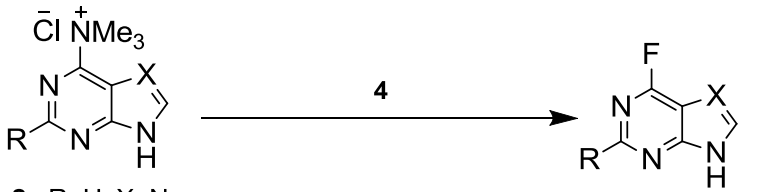
1a R=H, X=N
1b R=Cl, X=N
1c R=H, X=CH

2a R=H, X=N
2b R=Cl, X=N
2c R=H, X=CH

Product	R	X	Yield(%)[b]
2a	H	N	90
2b	Cl	N	90
2c	H	C	90

[a]rt = 30 ˚C. [b]isolated yields.

Table 2. Preparation of 6-fluoropurine and its 7-/9-unsubstituted analogues (**3a-3c**)



2a R=H, X=N
2b R=Cl, X=N
2c R=H, X=CH

3a R=H, X=N
3b R=Cl, X=N
3c R=H, X=CH

Entry	Product	**4**	Equiv. of **4**	Solvent	Temp. (˚C)[a]	Time (day)	Yield (%)[b]	Byproduct (%)[c]
1	**3a**	TBAF·3H_2O	1.5	DMSO	rt	1	18.0	0
2	**3a**	TBAF·3H_2O	3	DMSO	rt	1	24.6	0

3	**3a**	TBAF·3H$_2$O	4	DMSO	rt	1	24.7	0
4	**3a**	TBAF·3H$_2$O	3	DMF	rt	1	18.8	0
5	**3a**	TBAF·3H$_2$O	3	THF	rt	1	18.9	0
6	**3a**	TBAF·3H$_2$O	3	EtOH	rt	1	8.0	4.0
7	**3a**	TBAF·3H$_2$O	3	DMSO	50	1	13.7	10.0
8	**3a**	KF·2H$_2$O	3	DMSO	rt	1	2.8	1.1
9	**3a**	TBAF·3H$_2$O	3	DMSO	rt	4	53.5	0
10	**3a**	TBAF·3H$_2$O	3	DMSO	rt	7	71.3	0
11	**3a**	TBAF·3H$_2$O	3	DMSO	rt	14	80.0	3.8
12	**3b**	TBAF·3H$_2$O	3	DMSO	rt	0.5	90.0	0
13	**3c**	TBAF·3H$_2$O	3	DMSO	rt	0.5	91.0	0

[a]rt = 30 °C. [b,c]determined by HPLC analysis.

In order to find the optimized reaction conditions we first studied the preparation of 6-fluoropurine **3a** from **2a**. The results showed that **3a** was produced in a good yield of 71.3% with no byproduct within 7 days using 3 equivalents of TBAF·3H$_2$O as fluorinating agent in DMSO at room temperature (Entry 10). And the overall yield of **3a** (64.2%, Entry 10) was similar with that in method (v) (65%) but with a shorter reaction time (7.5 days *vs* 14 days) and less fluorinating agent (3 eq *vs* 4 eq).[16] In fact, our method will save more time. Because the preparation of TBAF$_{anh}$ needs 2 days under high vacuum (<0.1 mmHg)[16] which is hard to achieve, whereas TBAF·3H$_2$O is commercially available and cheap. When the reaction time prolonged to 14 days (Entry 11), the yield of **3a** increased to 80.0% and 3.8% byproduct was generated, probably by the hydrolysis of **3a**. **3a** was achieved in a better yield in DMSO than in DMF, THF and EtOH (Entries 2 and 4-6), and in a higher yield with TBAF·3H$_2$O than with KF·2H$_2$O (Entries 2 and 8), because of the good solubility of TBAF·3H$_2$O in DMSO. The reaction in

EtOH (Entry 6) gave a significant amount of byproduct, maybe because of EtOH also reacting with **2a**. When the temperature raised up to 50 ˚C (Entry 7), the reaction afforded **3a** in a reduced yield and byproduct in a considerable yield. And it was probably because of that **2a** started to decompose, water reacted with **2a** and the hydrolysis of **3a** was enhanced at 50 ˚C.

Then, we investigated the preparation of its 7-/9-unsubstituted analogues **3b** and **3c**, respectively. Compared with **3a** in Entry 10, **3b** and **3c** (Entries 12 and 13) were produced in better yields (90.0% and 91.0%), together with no byproducts within shorter reaction time (0.5 day) under the same reaction conditions, probably due to that the R = Cl in **2b** and X = C in **2c** (Table 2) increased the electrophilicity of the carbon atoms connecting to the trimethylammonio groups. We verified our point by the preparation of 6-fluoro-9*H*-purin-2-amine from 6-chloro-9*H*-purin-2-amine (Table 1, R = NH_2, X = N) through our route, ending up with a high yield of intermediate and no product. The overall yields of **3b** and **3c** in our report (Entries 12 and 13) were remarkably higher than reported. Because Entries 10, 12 and 13 produced no byproducts, the post-processing was simpler.

In conclusion, this paper described a new and convenient syntheses of 6-fluoropurine and its 7-/9-unsubstituted analogues, in which we first replaced the chlorine atoms with trimethylammonio groups which are better leaving groups, through the reaction of 6-chloropurine and its 7-/9-unsubstituted analogues with aqueous solution of trimethylamine, and then replaced the trimethylammonio groups with fluorine atoms using safe, commercially available and cheap TBAF·$3H_2O$ as fluorinating agent in DMSO at room temperature. The new method has advantages of milder conditions (compared with methods (i)-(v)), shorter reaction times (compared with method (v)), simpler post-processing (compared with methods (i)-(v)) and similar to higher yields (compared with methods (i)-(v)) compared with the reported methods.

EXPERIMENTAL

The melting points were obtained on a SGW X-4 microscopic melting point apparatus and were uncorrected. IR spectra were determined with a Bruker Tensor 27 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were determined in DMSO-d_6 using TMS as an internal reference with a Bruker Ascend^{TM} 400 NMR spectrometer operating at 400 MHz and 100 MHz, respectively. Low-resolution MS spectra (ESI) were measured by a Waters Quattro Premier XE spectrometer. High-resolution MS spectra (ESI) were measured by a Waters Q-TOF Premier spectrometer. TLC was carried out on TLC silica gel 60

F254 plates. Column chromatography was performed using silica gel (300-400 mesh, Qingdao Marine Chemical Ltd., Qingdao, China). HPLC was carried out on Agela Technologies LC-10F. All the commercially available reagents were used without further purification.

General Procedure for the Preparation of 2. To a solution of **1** (10 mmol) in THF (3 mL) at rt was slowly added 33% trimethylamine water solution (~3 mL, 30 mmol). When TLC (eluent: EtOAc) monitoring indicated that the reaction was completed (ca. 0.5 day) the crystalline precipitate was washed with ether and recrystallized from aqueous acetone (rt) giving **2**.

***N,N,N*-Trimethyl-9*H*-purin-6-aminium chloride (2a):** a pale-yellow solid; yield 90%; mp 201.5-202.5 ˚C (decomp.) (lit.,[15] 191-193 ˚C (decomp.)); IR (KBr) 1617, 1578 cm^{-1}; ^1H NMR δ 14.70 (s, 1H), 9.06 (s, 1H), 8.97 (s, 1H), 3.84 (s, 9H); ^{13}C NMR δ 156.6, 151.5, 150.4, 147.5, 123.3, 54.2; MS (ESI) *m/z* 178 $[M-Cl]^+$. HRMS (ESI) Calcd for $C_8H_{12}N_5$ $[M-Cl]^+$: 178.1093; Found: 178.1092.

2-Chloro-*N,N,N*-trimethyl-9*H*-purin-6-aminium chloride (2b): a pale-yellow solid; yield 90%; mp > 300 ˚C (lit.,[15] > 300 ˚C); IR (KBr) 1612, 1561 cm^{-1}; ^1H NMR δ 14.88 (s, 1H), 8.98 (s, 1H), 3.81 (s, 9H); ^{13}C NMR δ 154.5, 152.3, 152.1, 138.4, 117.9, 54.4; MS (ESI) *m/z* 212 $[M-Cl]^+$. HRMS (ESI) Calcd for $C_8H_{11}N_5Cl$ $[M-Cl]^+$: 212.0703; Found: 212.0702.

***N,N,N*-Trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-aminium chloride (2c):** a white solid; yield 90%, mp 191.2-192.2 ˚C; IR (KBr) 1604, 1565 cm^{-1}; ^1H NMR δ 13.21 (s, 1H), 8.89 (s, 1H), 8.00 (d, 1H, *J* = 3.4 Hz), 7.22 (d, 1H, *J* =3.4 Hz), 3.76 (s, 9H); ^{13}C NMR δ 155.1, 154.7, 148.7, 130.4, 107.2, 99.6, 54.2. MS (ESI) *m/z* 177 $[M-Cl]^+$. HRMS (ESI) Calcd for $C_9H_{13}N_4$ $[M-Cl]^+$: 177.1140; Found: 177.1141.

General Procedure for the Preparation of 3. As indicated in Table 2, to a solution of **2** (1.2 mmol) in solvent (3 mL) at the temperature was added fluorinating agent. The reaction was maintained at that temperature for the time indicated in Table 2 and was monitored by HPLC. When the reaction was terminated, add water (30 mL) into the reaction mixture and extract it with EtOAc five times (10 mL each). The combined extracts were washed with water and brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuum. In Entries 6, 7, 8 and 11, the residue was purified by silica gel column chromatography.

6-Fluoro-9*H*-purine (3a): a white solid; mp 125.5-126.6 ˚C (lit.,[13] 122-124 ˚C); IR (KBr) 1634, 1578 cm^{-1}; ^1H NMR δ 13.98 (s, 1H), 8.68 (s, 1H), 8.65 (s, 1H); ^{13}C NMR δ 158.4 (*J* = 214.7 Hz), 151.1, 151.0, 145.7, 118.7; MS (ESI) *m/z* 137 $[M-H]^-$. HRMS (ESI) Calcd for $C_5H_4N_4F$ $[M+H]^+$: 139.0420; Found: 139.0422.

2-Chloro-6-fluoro-9*H*-purine (3b): a white solid; mp 146.0-148.2 ˚C (lit.,[15] 146 ˚C); IR (KBr) 1656, 1634, 1565 cm^{-1}; ^1H NMR δ 14.01 (s, 1H), 8.72 (s, 1H); ^{13}C NMR δ 157.8 (*J* = 207.1 Hz), 149.9, 149.8, 146.9, 117.8; MS (ESI) *m/z* 171 $[M-H]^-$. HRMS (ESI) Calcd for $C_5H_3N_4FCl$ $[M+H]^+$: 173.0030; Found: 173.0029.

4-Fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidine (3c): a white solid; mp 172.8-173.8 ˚C; IR (KBr) 1629, 1594, 1576 cm^{-1}; ^1H NMR δ 12.61 (s, 1H), 8.49 (s, 1H), 7.66 (d, 1H, *J* = 3.0 Hz), 6.66 (d, 1H, *J* = 3.0 Hz). ^{13}C NMR δ 161.4 (*J* = 197.8 Hz), 155.5 (*J* = 9.9 Hz), 149.8 (*J* = 11.1 Hz), 127.5, 103.1 (*J* = 26.2 Hz), 96.9 (*J* = 4.1 Hz); MS (ESI) *m/z* 136 $[M-H]^-$. HRMS (ESI) Calcd for $C_6H_5N_3F$ $[M+H]^+$: 138.0468; Found: 138.0465.

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