HETEROCYCLES, Vol.55, No.3, pp.461 - 464, Received, 11th December, 2000

A NEW SANDMEYER IODINATION OF 2-AMINOPURINES IN NON-AQUEOUS CONDITIONS: COMBINATION OF ALKALI METAL IODIDE AND IODINE AS IODINE SOURCES

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Abstract — An effective method for iodination using 2-aminopurines in non-aqueous conditions was found. The optimal conditions involved the combination of isopentyl nitrite, cuprous iodide, alkali metal iodide and iodine in ethylene glycol dimethyl ether at 60℃.

4-[6-Amino-8-(3-fluorophenyl)-9-methyl-9*H*-purin-2-yl]]-2-methylbut-3-yn-2-ol hydrochloride (E3141) is a novel adenosine antagonist which could have potential use as a remedy for non-insulin dependent diabetes mellitus based on a new mechanism of action.[1] The structure of E3141 has an acetylene side chain connected to 2-position of the purine ring (adenine), thus the introduction of the acetylene side chain is one of the key points of its synthesis. In general, the Heck-Sonogashira reaction[2, 3] is employed for the synthesis of aryl-acetylene from the aryl iodide and the acetylene group. The coupling reaction of 6-chloro-8-(3-fluorophenyl)-2-iodo-9-methyl-9*H*-purine (**1**) with 3-methyl-1-butyn-3-ol has a high yield.[1] However, in order to use this method it is necessary to synthesize **1** efficiently. The introduction of the iodine atom only at 2-position is efficiently achieved by a Sandmeyer reaction[4] which involves the diazotization of 6-chloro-8-(3-fluorophenyl)-9-methyl-9*H* -purin-2-amine (**2)** (Figure 1)

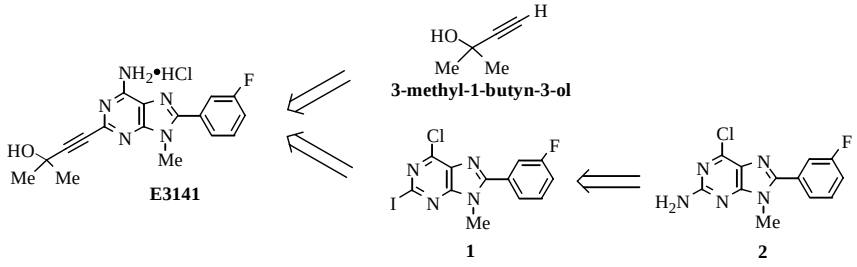
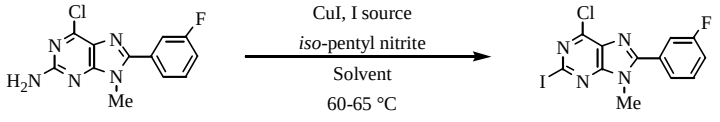


Figure 1. Synthetic strategy

In general, diazotization of aromatic amines is achieved by using sodium nitrite in the presence of mineral acids[5] in aqueous medium. However, **2** could not be diazotized by conventional methods that employ aqueous conditions because of its insolubility. Among the diazotization reactions which use anhydrous conditions,[6] alkyl nitrites are the most frequently

employed.[7] Nair and Richerdson[8] have reported that 6-chloro-2-iodopurine nucleoside was formed by diazotization-substitution of 2-amino-6-chloropurine nucleoside with *n*-pentyl nitrite in diiodomethane (CH_2I_2) acting as both an iodine source and a solvent. More recently, Matsuda *et al*.[9] reported that the same 2-iodopurine nucleoside was synthesized by Sandmeyer iodination of 2-amino-6-chloropurine nucleoside with isopentyl nitrite, CH_2I_2, iodine (I_2), cuprous iodide (CuI) in acetonitrile (MeCN) or tetrahydrofuran (THF). However, CH_2I_2 is expensive and harmful to the environment, and the reaction using MeCN or THF as a solvent promoted the formation of a by-product. Thus, we decided to look for Sandmeyer iodination method for 2-aminopurine **(2)** which satisfied the following conditions; 1) it did not require CH_2I_2, 2) it used a relatively inexpensive reagent, 3) the generation of by-products could be controlled, 4) scale up was possible.

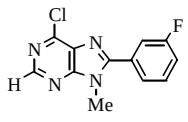
Alkali metal iodides are inexpensive reagents which can be used instead of CH_2I_2 as iodine sources. Although a few methods[10] that use alkali metal iodide in non-aqueous conditions have been reported so far, we thought that the reaction might also proceed by the combination of a suitable alkali metal iodide and solvent. Initially, we investigated the effectiveness of alkali metal iodides as iodine sources. LiI, NaI,[10] KI,[11] RbI and CsI were chosen as alkali metal iodides in this study considering availability and price. The results obtained are shown in Table 1.



2 **1**

Entry	I source (mol equiv.)	CuI (mol equiv.)	Solvent	Time (h)	Conversion[a] **1** (%)	**3** (%)	**4** (%)	Yield[b] (%)
1	CH_2I_2 (10) + I_2 (1)	1.0	DME	1.5	73	4		70
2	LiI (1) + I_2 (0.5)	1.0	DME	1.5	69	8		68
3	NaI (1) + I_2 (0.5)	1.0	DME	1.5	77	6		71
4	KI (1) + I_2 (0.5)	1.0	DME	1.5	78	8		75
5	RbI (1) + I_2 (0.5)	1.0	DME	1.5	75	7		72
6	CsI (1) + I_2 (0.5)	1.0	DME	1.5	87	8		84
7	CsI (1) + I_2 (0.5)	0.3	DME	1.5	88	9		85
8	CsI (1) + I_2 (0.5)	0.3	THF	2.0	77	13		74
9	CsI (1) + I_2 (0.5)	0.3	CH_3CN	1.0	50	0.2	27	47
10	CsI (2)	0.3	DME	1.5	47	26		45
11	I_2 (2)	0.3	DME	1.0	67	23		64

[a] Conversion was calculated by using the HPLC area of **1** in the reaction mixture. [b] Isolated yields.



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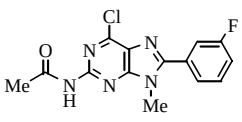

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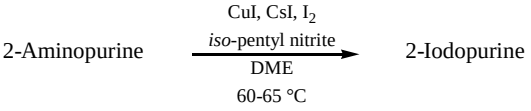
Table 1. Synthesis of the 2-iodopurine **(1)** from 2-aminopurine **(2)**

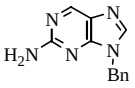
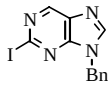
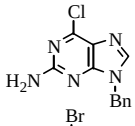
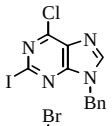
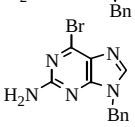
Under the Matsuda's condition, the 2-aminopurine **(2)** required an excess CH_2I_2 to give the 2-iodopurine **(1)** in 70% yield (Entry 1). Because of the relatively good solubility of **2** in

dimethoxyethane (DME) compared to other aqueous and non-aqueous solvents it was used as the solvent for this reaction. Furthermore, alkali metal iodides dissolve in DME comparatively well, making it suitable for this reaction. Using the alkali metal iodides, the target iodide **(1)** was obtained by using only 1 equivalent of alkali metal iodide and the yield was equal or better than that using CH_2I_2 (Entries 2-6). In particular, CsI was found to be the most effective (84% yield, Entry 6) among the alkali metal iodides. It was also found that the quantity of CuI could be reduced to 0.3 equivalents (Entry 7). When the reaction was performed in THF, the yield of **1** was moderate and 13% of 6-chloro-8-(3-fluorophenyl)-9-methyl-9*H*-purine **(3)**[12] was obtained as a by-product (Entry 8). In MeCN, the yield of **1** was decreased even further and 6-chloro-8-(3-fluorophenyl)-9-methyl-9*H*-purin-2-acetoamide **(4)**[13] was obtained as a by-product (Entry 9). When CsI or I_2 was used alone as a iodine source, the generation of reductive compound **(3)** was increased (Entries 10 and 11). Accordingly, it was concluded that the combination of CsI and I_2 was important in order to promote the reaction smoothly.

Under the conditions determined above, we synthesized **2** in the 16 kg scale and demonstrated that this reaction was industrially viable.

Next, we explored the applicability of this reaction conditions to several 2-aminopurine compounds. In all cases, the 2-aminopurine compound gave the target 2-iodopurine compound in good yield as shown in Table 2.



Entry	2-Aminopurine	Time (h)	2-Iodopurine	yield (%)[a]
1		4		78
2		3		78
3		6		74

[a] Isolated yields.

Table 2. Synthesis of the 2-iodopurine compounds

In summary, we found that the Sandmeyer iodination using CsI (1 mol eq.) and I_2 (0.5 mol eq.) as iodine sources instead of CH_2I_2, was an efficient system for transforming the water-insoluble 2-aminopurine compounds to 2-iodopurine compounds in DME under non-aqueous conditions. The present method gave a good yield, and was easy to manipulate, harmless to the environment, and viable for industrial scale up which are distinct advantages over conventional methods. However, it was not possible to clarify how alkali metal iodides including CsI were involved in the reaction. The reaction mechanism and its application to

aryl amines in general are under investigation.

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12. Since the 6-amino group of adenosine derivative was reductively deaminated to nebularine derivatives in THF with n-pentyl nitrite,[14] the reductive deamination of the 2-amino group of **2** can be explained by a similar mechanism.
13. This compound may be formed by reaction of the proposed 2-purinyl radical intermediate of the diazotization reaction[8, 15] with MeCN, followed by H_2O addition.
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16. The general procedure of our method is as follows; isopentyl nitrite (2.9 mL, 21.8 mmol) was added to a mixture of 6-chloro-8-(3-fluorophenyl)-9-methyl-9*H*-purin-2-amine (**2**, 1.0 g, 3.6 mmol), CsI (0.94 g, 3.6 mmol), I_2 (0.46 g, 1.8 mmol), and CuI (0.21 g, 1.1 mmol) in DME (20 mL). The mixture was heated at 60-65°C for 1.5 h, and then cooled to rt. Insoluble materials were removed by filtration, and the filtrate was diluted with toluene (30 mL), washed with 25% aq. NH_3 (10 mL x 2), 5% aq. $Na_2S_2O_3$ (10mL) and then 5% aq. NaCl (5 mL), dried over $MgSO_4$, followed by evaporation of the solvent to give a slightly yellowish white solid. The solid was crystallized from toluene (10 mL) and *n*-heptane (20 mL) at 0°C, filtered, and then washed with toluene (10 mL) to give 6-chloro-8-(3-fluorophenyl)-2-iodo-9-methyl-9*H*-purine (**1**, 1.19 g, 85 %) as white powder: mp 185.7°C (recrystallized from toluene : *n*-heptane = 1 : 2). ^{1}H NMR (DMSO-d_6, 400 MHz): □ (ppm) 3.89 (s, 3H), 7.49-7.56 (m, 1H), 7.66-7.72 (m, 1H), 7.76-7.82 (m, 2H). MS: (FAB) 389 (MH^+).