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RESEARCH ARTICLE

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Direct C−H Arylation of Purine on Solid Phase and Its Use for Chemical Libraries Synthesis

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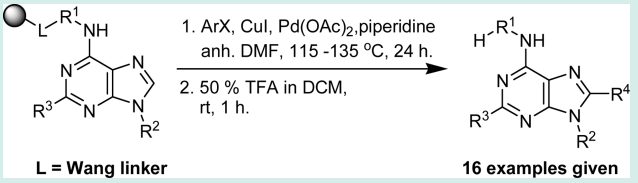
Supporting Information

ABSTRACT: C^8−H direct arylation of purine derivatives immobilized on Wang resin is described. The purine skeleton was immobilized via C^6-regioselective substitution of 2,6-dichloropurine with polymer-supported amines. After N^9-alkylation with two different alkyl iodides and C^2 substitution with two selected amines, reaction conditions for C^8−H arylation were developed and optimized. Various aryl bromides and aryl iodides were used for the reaction affording the target 2,6,8,9-tetrasubstituted purines in very good purity. The same reaction conditions were also applied for the synthesis of 2,6,8-trisubstituted purines, however, yields were lower. The methodology is applicable for high throughput synthesis of chemical libraries comprised of purine scaffold.



KEYWORDS: purines, coupling reaction, Pd catalyst, direct arylation, solid-phase synthesis

INTRODUCTION

2,6,9- or 2,6,8-Trisubstituted and 2,6,8,9-tetrasubstituted purines, as well as non-natural nucleosides have been largely studied for their wide range of biological activities.[1,2] Research in this area is very intensive and many new and interesting results appeared recently. C^8-modified purine derivatives were reported, for example, as effective inhibitors of glycogen synthase kinase,[3] adenosine A2A receptor antagonists[4] or selective cannabinoid type 1 receptor antagonist.[5]

The tri- or tetra-substituted purines are prepared either by heterocycle assembly[6−8] leading to target structures or decoration of purine with suitable building blocks (e.g., nucleophilic substitution[9] or metal mediated reactions[10−12]). The synthesis of C^8-arylated derivates was described by heterocycle assembly with use of solution and solid-phase synthesis.[13−15] Decoration of the purine scaffold with use of cross-coupling reactions from appropriate C^8-halogenated derivatives was described for synthesis in solution[16,17] and for solid-phase synthesis as well.[18,19]

Direct arylation is an efficient and suitable method for formation of a regioselective C−C bond in one step.[20,21] Recently, Čerňa et al.[22] and Storr et al.[23,24] independently introduced a direct C−H arylation in solution as an alternative preparation of C^8-arylated purine bases and nucleosides.[25] In addition, these methods, in combination with cross coupling reaction led to the preparation of small libraries of various 2,6,8,9-tetrasubstituted purines[16,22] and fused purine systems.[26] Direct C^8−H arylation of solid-supported heterocyclic scaffold has not yet been studied, only the direct arylation of imidazotriazines on solid phase was reported recently.[27]

In this paper, we describe an expeditious and efficient methodology for solid-phase synthesis of 2,6,8-tri or 2,6,8,9-tetrasubstituted purine derivatives using direct C^8−H arylation, following two nucleophilic substitutions and optionally *N*-alkylation to access derivatives with three or four diverse positions. In combination with solid-phase synthesis it can be used as a powerful tool for high-throughput synthesis of chemical libraries, especially because of (i) simple isolation of intermediates during the multistep synthesis, (ii) rapid preparation of a large number of chemical entities, and (iii) the possibility of using a limited number of reaction vessels, when a split-and-pool method is used.[28]

RESULTS AND DISCUSSION

The synthesis was carried out on Wang resin using three different types of anchoring to demonstrate the resulting diversity in position 6 of the purine scaffold: 1,3-diaminopropane was attached via carbamate linkage using the carbonyldiimidazole (CDI) activation method.[29] 2-(Fmoc-amino)ethanol (Fmoc = 9-fluorenylmethyloxycarbonyl) was linked via an ether structure using trichloroacetimidate activation[30] and two protected Fmoc amino acids (Fmoc-β-Ala-OH and Fmoc-γ-ABU-OH) were immobilized via an ester bond by the Mitsunobu procedure[31] according to Scheme 1. The building blocks for furnishing resins **1** were selected to afford variously functionalized aliphatic chains in position 6.

After the immobilization, the resin-bound primary amines **1** were converted to trisubstituted derivatives **4** with using a protocol described previously[32] (Scheme 2). Building blocks

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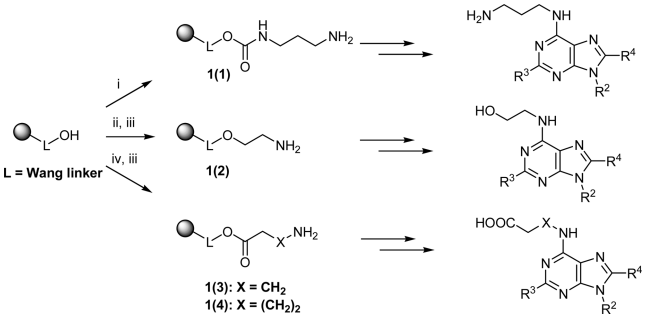
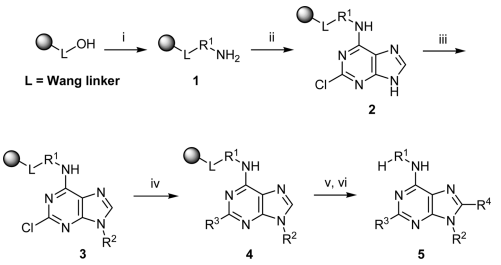
Scheme 1. Methods of Amino Derivative Immobilization[a]



[a] Reagents and conditions: (i) CDI, pyridine, DCM, 2 h, then 1,3-diaminopropane, DCM, 2 h; (ii) trichloroacetonitrile, DBU, DCM, 2 h, then Fmoc-aminoethanol, $BF_3 \cdot Et_2O$, THF 1 h; (iii) 20% piperidine in DMF, 20 min; (iv) Fmoc-amino acid, PPh_3, DIAD, anhydrous THF, 1 h.

Scheme 2. Preparation of Target Purines[a]



[a] Reagents and conditions: (i) according Scheme 1; (ii) 2,6-dichloropurine, DIEA, THF, 50 °C, 14 h; (iii) alkyl iodide, DBU, DMSO, 50 °C, 14 h (iv) piperidine or 3-aminopropanol, diethylene glycol diethyl ether, 150 °C, 24 h; (v) aryl halide, CuI, $Pd(OAc)_2$, piperidine, anhydrous DMF, 115 °C, 24 h (aryl iodide) or 48 h (aryl bromide); (vi) 50% TFA in DCM, 1 h.

used to introduce substituents R^1−R^4 are portrayed in Figure 1. Notation of the individual compounds is based on used building blocks.

The displacement of the chlorine atom at purine C^2 by amines required high temperature (150 °C) to proceed and led to decrease of the yield of derivates **4**(**3**,$\mathbf{R^2}$,$\mathbf{R^3}$) and **4**(**4**,$\mathbf{R^2}$,$\mathbf{R^3}$) due to competing aminolysis of the ester bond and partial cleavage of intermediates from the resin. For this reason the final products **5**(**3**,$\mathbf{R^2}$,$\mathbf{R^3}$,$\mathbf{R^4}$) and **5**(**4**,$\mathbf{R^2}$,$\mathbf{R^3}$,$\mathbf{R^4}$) were isolated in yields of only 7−25% (see Table 1).

Direct C^8−H Arylation of 2,6,9-Trisubstituted Purines. The C^8−H arylation was tested with use of phenyl iodide, palladium acetate, and copper(I) iodide under various conditions (type of base, concentration of aryl iodide, temperature, and solvent were varied).

First, we tested the direct arylation of the intermediate **4**(**1**,**1**,**1**) in anhydrous DMF and anhydrous dioxane using Cs_2CO_3 as the base. However, the reaction did not furnish satisfactory conversion (max. about 60%, HPLC-UV traces) although temperatures from 90 to 110 °C and various concentrations of aryl iodide were tested. In addition, complete removal of Cs_2CO_3 from the resin was problematic. This problem was solved by addition of piperidine. The reaction was tested in anhydrous DMF and anhydrous dioxane at elevated temperature (90−115 °C) and various concentrations of aryl iodides. While

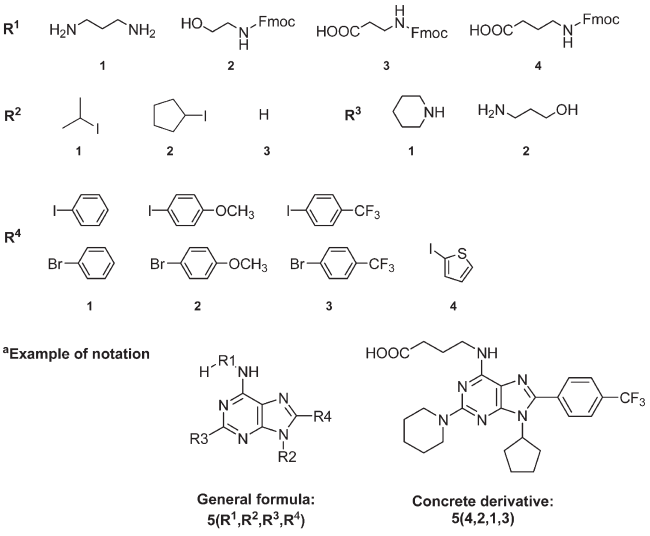


Figure 1. Building blocks and notation of the final structures.

Table 1. Summary of the Prepared Products

Entry	Code of structure	H-R^1	R^2	R^3	R^4	Purity[a]	Yield[b]
1	5(1,1,1,1)					94%	61%
2	5(1,1,1,2)					95%	52%
3	5(1,1,1,3)					90%	70%
4	5(1,2,1,2)					80%	33%
5	5(2,1,1,1)					90%	42%
6	5(2,1,1,2)					91%	35%
7	5(2,1,1,3)					91%	52%
8	5(4,1,1,1)					96%	7%
9	5(4,2,1,2)					91%	15%
10	5(3,1,1,3)					92%	25%
11	5(2,1,2,1)					61%	16%
12	5(1,1,2,3)					62%	18%
13	5(1,1,1,4)					42%	15%
14	5(1,1,1,bis4)					37%	12%
15	5(2,3,1,3)		H			71%	21%
16	5(2,3,1,1)		H			60%	20%
17	5(1,3,1,1)		H			58%	14%

[a] Purity of crude final product after the entire reaction sequence; integrated HPLC-UV traces. [b] Overall yields of compounds **5** after the all reaction steps and HPLC purification.

the direct arylation in anhydrous dioxane provided maximally 5% of product (HPLC-UV traces), substantially better results were obtained in anhydrous DMF with 0.8 M of PhI solution at 115 °C after 24 h, when the arylation was quantitative and we obtained product **5**(**1**,**1**,**1**,**1**) in very good purity (94%, HPLC-UV traces). Decreasing the concentration of aryl iodide to 0.2 or 0.4 M under the same reaction conditions lowered the purity to 80%, and the reaction had to be repeated to drive it to completion.

The C^8−H arylation of 2,6,9-trisubstituted purines with using an already-developed procedure (0.8 M of PhI solution, CuI, piperidine, $Pd(OAc)_2$, anhydrous DMF, 115 °C, 24 h) was very effective. The protocol was successfully tested for unsubstituted phenyl iodide, and phenyl iodides substituted by electron-donating

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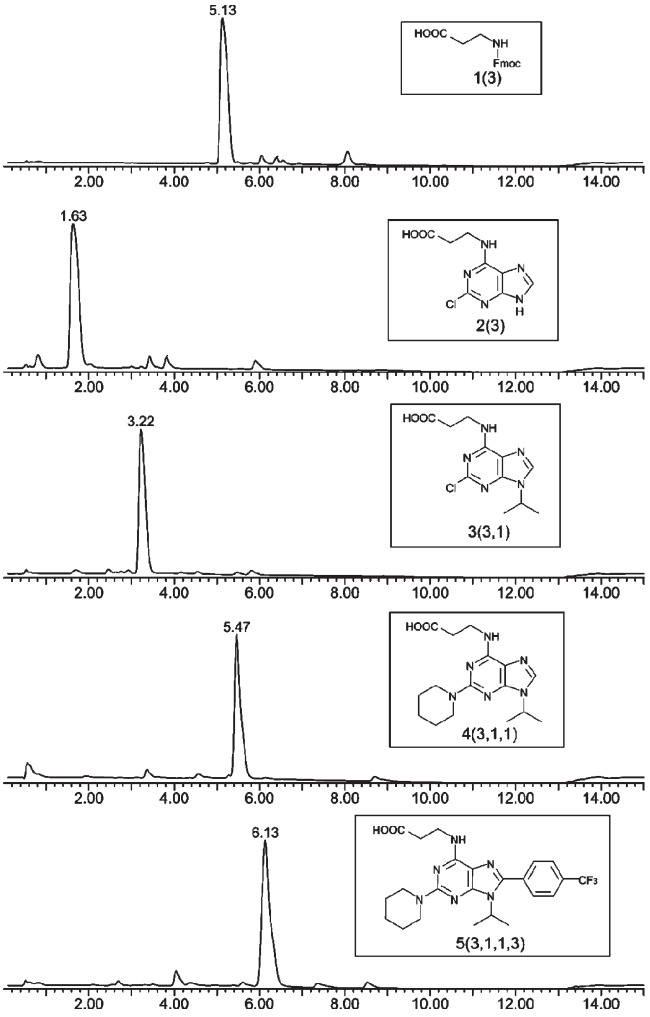


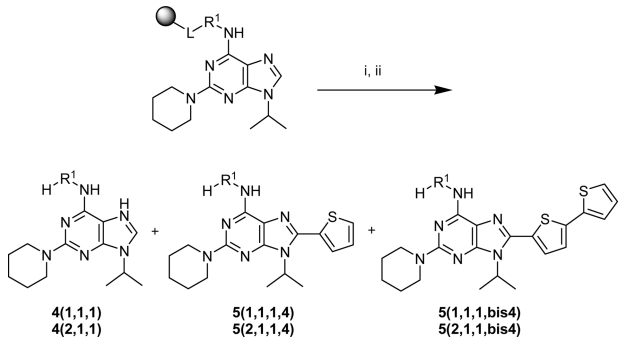
Figure 2. Example of HPLC traces of crude intermediates leading to target compound **5**(**3**,**1**,**1**,**3**). The analyses were performed after cleavage from resin with trifluoroacetic acid. The intermediate **1**(**3**) was analyzed before removing the Fmoc group.

as well as electron-withdrawing functional groups (see Table 1, entries 1−10). Building blocks are depicted in Figure 1. The purity of crude products was excellent after each reaction step (see example in Figure 2), except for derivatives substituted on position 2 by 3-amino-propan-1-ol, where the reaction mixture contained a number of side products(see Table 1, entries 11 and 12).

The overall yields of the corresponding products **5** after cleavage from the resin and semipreparative HPLC purification varied from 7 to 70% (see Table 1). As mentioned before, derivatives **5**(**3**,$\mathbf{R^2}$,**1**,$\mathbf{R^4}$) and **5**(**4**,$\mathbf{R^2}$,**1**,$\mathbf{R^4}$) were obtained in lower yield due to partial cleavage from the resin during the displacement of chlorine with amines (Scheme 2, step ii) and arylation affording derivatives **5**($\mathbf{R^1}$,$\mathbf{R^2}$,**2**,$\mathbf{R^4}$) was accompanied with number of side products.

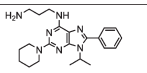
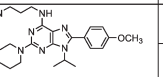
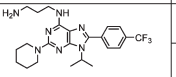
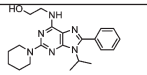
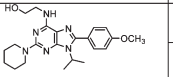
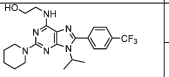
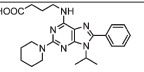
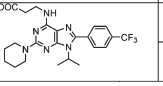
Coupling reaction of derivative **4**(**1**,**1**,**1**) with 2-iodothiophene as representative heterocycle (0.8 M 2-iodothiophene; CuI, $Pd(OAc)_2$, piperidine, anhydrous DMF, 115 °C, 24 h.) yielded 35% of the product **5**(**1**,**1**,**1**,**4**) accompanied by 10% of a side product **5**(**1**,**1**,**1**,**bis4**) and 55% of starting material (HPLC-UV traces). Repeating the arylation increased the yield of the desired product **5**(**1**,**1**,**1**,**4**), as well as side product **5**(**1**,**1**,**1**,**bis4**) (see

Scheme 3. C^8−H Arylation with 2-Iodothiophene[a]



[a] Reagents and conditions: (i) 2-iodothiophene, $Pd(OAc)_2$, CuI, piperidine, anhydrous DMF, 115 °C, 24 h; (ii) 50% TFA in DCM, 1 h.

Table 2. Comparison of Methods of Preparation

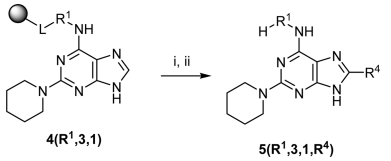
Entry	Code of structure	Target structure of purine	Method[a]	Purity[b]
1	5(1,1,1,1)		A	94%
2			B	98%
3	5(1,1,1,2)		A	95%
4			B	95%
5	5(1,1,1,3)		A	90%
6			B	98%
7	5(2,1,1,1)		A	90%
8			B	87%
9	5(2,1,1,2)		A	91%
10			B	80%
11	5(2,1,1,3)		A	91%
12			B	76%
13	5(4,1,1,1)		A	96%
14			B	90%
17	5(3,1,1,3)		A	92%
18			B	90%

[a] Reaction time: method A, 24 h; method B, 48 h. [b] Purity of crude final product after the all reaction sequence; integrated HPLC−UV traces.

Table 1), but the starting material **4**(**1**,**1**,**1**) was still incompletely transformed. Optimization of the reaction conditions by varying 2-iodothiophene concentration and temperature did not improve the yield of the product **5**(**1**,**1**,**1**,**4**). The mono **5**(**1**,**1**,**1**,**4**) and double **5**(**1**,**1**,**1**,**bis4**) arylated compounds were isolated and their structure was confirmed by NMR spectroscopy and HRMS. The arylation of a substrate **4**(**2**,**1**,**1**) with 2-iodothiophene yielded an analogous mixture of products (see Scheme 3).

In addition to aryl iodides (method A), we also successfully tested commercially available cheaper aryl bromides (method B), such as 4-methoxyphenyl bromide, 4-trifluoromethylphenyl bromide, and phenyl bromide. Because of their lower reactivity, the reaction time was prolonged to 48 h but other reaction conditions were identical giving the final products in purity ranging from 90 to 95% according to HPLC-UV (see Table 2). Due to a

Scheme 4. Preparation of N^9-Unsubstituted Compounds[a]



[a] Reagents and conditions: (i) aryl iodide, CuI, $Pd(OAc)_2$, piperidine, anhydrous DMF, 135 °C, 48 h; (ii) 50% TFA in DCM, 1 h.

longer reaction time for aryl bromides, versus aryl iodides, all preparative reactions in this study were performed with aryl iodides (method A).

Direct C^8−H Arylation of 2,6-Disubstituted Purines. We also tested C^8−H arylation of N^9-unsubstituted purines (Scheme 4), which can be subsequently converted to a C^8-modified purine nucleosides. Unfortunately, the presence of the acidic hydrogen on purine N^9 decreased reactivity toward arylation. A very low conversion (about 10%, HPLC-UV traces) was observed under the previously described conditions. Increasing the concentration of aryl iodide or piperidine or both did not improve the conversion (only 10% to 20%).

When higher temperature was used (135 °C), the arylation proceeded significantly better. However, we did not observe quantitative reaction; the best purity (71%) was achieved for derivative **5(2,3,1,3)** (HPLC-UV traces). For this reason N^9-unsubstituted purines were isolated after HPLC purification in 14 to 21% yield.

CONCLUSION

We developed a solid-phase synthesis for direct C^8−H arylation of purine derivatives. The versatility of the method was documented by the preparation, isolation and characterization of fourteen 2,6,8,9-tetrasubstituted purines. An optimized reaction sequence provided target compounds in very good purity. The conditions were evaluated for aryl iodides as reactants, but aryl bromides were also found to be applicable as reactants though reaction times were prolonged. The method was applied, also, for the synthesis of 2,6,8-trisubstituted compounds (three examples are given). Although the isolated yields of individual chemical entities are not quantitative, the, method is suitable for high-throughput synthesis of chemical libraries from commercially available synthons to afford, rapidly, a set of compounds for biological screening. The, method thus represents an additional tool for systematic biological study of purine derivatives using combinatorial chemistry.

ASSOCIATED CONTENT

Supporting Information. General information, analytical data, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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