# Direct Arylation of Purine on Solid Phase and Its Use for Chemical Libraries

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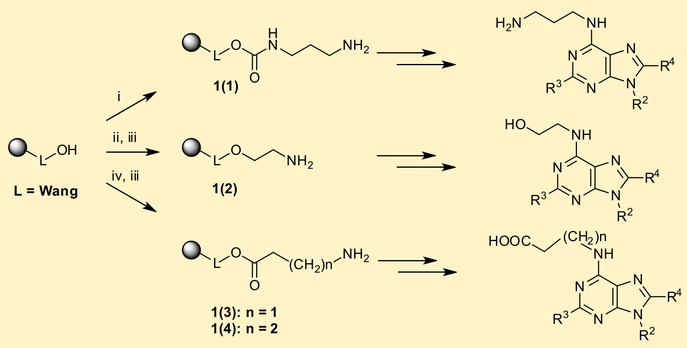
Direct arylation is an efficient and suitable method for formation of a regioselective C-C bond in one step. In this research we described an expeditious and efficient methodology for solid-phase synthesis of 2,6,8-tri or 2,6,8,9-tetrasubstituted purine derivatives using direct C8-H arylation following 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.

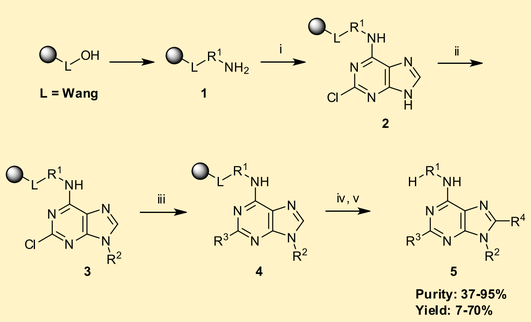
**Scheme 1:** Immobilization of the first building block



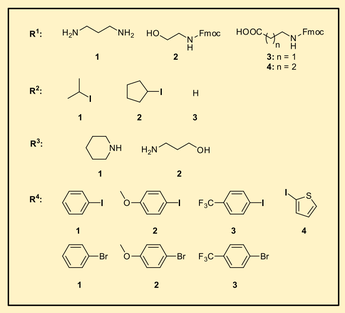

Reagents and conditions (i) CDI, pyridin, DCM, 2 h, rt, then 1,3-diaminopropane, DCM, 2 h, rt; (ii) trichloracetonitril, DBU, DCM, 2 h, rt, then Fmoc-aminoethanol, BF3·Et2O, THF 1 h, rt; (iii) 20% piperidin v DMF, 20 min, rt; (iv) Fmoc-amino aci, PPh3, DIAD, anhydrous THF, 1 h, rt.

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. 2-(Fmoc-amino)ethanol (Fmoc = 9-fluorenylmethyloxycarbonyl) was linked via an ether structure using trichloroacetimidate activation 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 according to Scheme 1. The building blocks for furnishing resins **1** were selected to afford variously functionalized aliphatic chains in position 6.

**Scheme 2:** Preparation of target compounds.




Successfully used building blocks.



Reagent and conditions: (i) 2,6-dichlorpurine, EDIPA, THF, 50°C, 14 h; (ii) alkyl jodide, DBU, DMSO, 50 °C, 14 h (iii) piperidine or 3-aminopropanol, diethylene glycol diethyl ether, 150°C, 24 h; (iv) aryl jodide, CuI, Pd(OAc)2, piperidin, bezvodý DMF, 115°C, 24 h. (or 48 h for aryl bromides); (v) 50% TFA v DCM, 1 h, rt.; (vi) aryl jodide, CuI, Pd(OAc)2, piperidin, bezvodý DMF, 135 °C, 48 h.

After the immobilization, the resin-bound primary amines **1** were converted to trisubstituted derivatives **4** with using a protocol described in our previous research (Scheme 2). The displacement of the chlorine atom at purine C2 by amines required high temperature (150 ° C) to proceed and led to decrease of the yield of some derivates. The C8-H arylation of 2,6,9-trisubstituted purines with using our developed procedure was very effective. The protocol was successfully tested for unsubstituted phenyl iodide, and phenyl iodides substituted by electron-donating as well as electron-withdrawing functional groups. The purity of crude products was excellent after each reaction step, except for derivatives substituted on position 2 by 3-amino-propan-1-ol, where the reaction mixture contained a number of side products. The overall yields of the corresponding products **5** after cleavage from the resin and semipreparative HPLC purification varied from 7 to 70%

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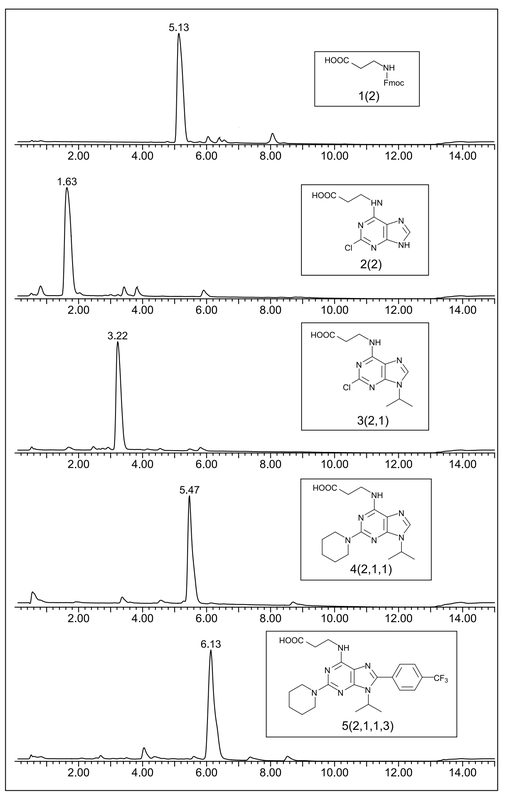
**Figure 1:** HPLC traces of crude intermediates




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

**Figure 2:** Successfully tested methods

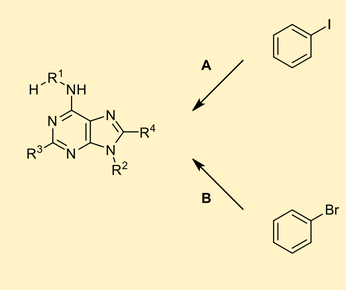
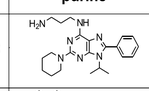
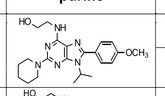
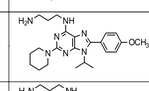
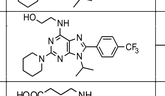
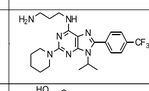
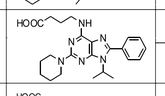
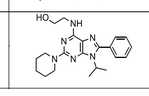
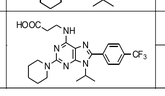



**Table 1:** Comparison of the method A and B

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

We also tested C8-H arylation of N9-unsubstituted purines, which can be subsequently converted to a C8-modified purine nucleosides. Unfortunately, the presence of the acidic hydrogen on purine N9 decreased reactivity toward arylation. When higher temperature was used, 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). For this reason N9-unsubstitutedpurines were isolated after HPLC purification in 14 to 21% yield. All the compounds were subjected to MTT cytotoxicity screening. Some of derivatives provided activity at micromolar concentration, but they also had a high toxicity. However the terapeutic index of some derivatives were observed in units order.

**Table 2:** Results of the MTT cytotoxicity test.

| Compound | CEM | CEM - DNR | K562 | K562 - TAX | A549 | HCT116 p53WTP | HCT116 53MUT | BJ | MRC-5 |
|---|---|---|---|---|---|---|---|---|---|
| 5(2,1,1,2) | 98,7 | 100 | 88,7 | 100 | 97,5 | 100 | 100 | 100 | 75,2 |
| 5(1,1,1,2) | 3,1 | 1,8 | 1,1 | 1,1 | 3,7 | 2,8 | 2,6 | 4 | 3,3 |
| 5(2,1,1,3) | 88,9 | 100 | 73,9 | 100 | 99,6 | 100 | 95,5 | 100 | 45,3 |
| 5(1,2,1,2) | 1,9 | 3,4 | 1,6 | 1,2 | 3,6 | 3,7 | 2,8 | 36 | 3,9 |
| 5(1,1,1,3) | 1 | 1,4 | 1,5 | 0,97 | 3,2 | 1,2 | 1,4 | 3,9 | 4 |
| 5(1,1,1,1) | 1,9 | 3,3 | 1,2 | 3,5 | 4 | 3,4 | 3,7 | 4 | 4,1 |
| 5(3,1,1,3) | 14,4 | 18,5 | 16,8 | 16,1 | 19,5 | 19 | 18,7 | 49,6 | 43,9 |
| 5(4,2,1,2) | 16 | 37,4 | 20,9 | 18,5 | 27,1 | 26,7 | 18,1 | 63,2 | 67,5 |
| 5(4,1,1,1) | 37,9 | 59,9 | 45,7 | 48,3 | 63,6 | 55 | 42,9 | 90,8 | 80,1 |
| 5(2,3,1,3) | 1,3 | 11,9 | 7,6 | 11,2 | 21,5 | 20 | 25,1 | 46,4 | 63,1 |
| 5(2,3,1,1) | 10,4 | 15,3 | 8,3 | 14,7 | 18,4 | 31,5 | 15,1 | 14,6 | 56,3 |
| 5(1,3,1,1) | 6,4 | 12,1 | 2,8 | 8,7 | 12,9 | 6 | 6,9 | 10,1 | 14,1 |
| 5(1,1,1,4) | 1,5 | 1,5 | 0,99 | 0,98 | 3,9 | 2,1 | 2 | 4,3 | 3,4 |
| 5(1,1,1,bis4) | 2,8 | 3,7 | 1,9 | 3,5 | 4 | 4,4 | 3,6 | 4,3 | 3,8 |
| 5(2,1,1,1) | 17,9 | 35,2 | 18,8 | 45,5 | 43,1 | 22,3 | 45,3 | 71,5 | 36,4 |
| 5(1,3,1,2) | 2,8 | 4,3 | 1,2 | 3,6 | 3,8 | 1,3 | 3,6 | 3,5 | 3,6 |

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