

Selective Synthesis of 7-Substituted  
Purines via 7,8-Dihydropurines

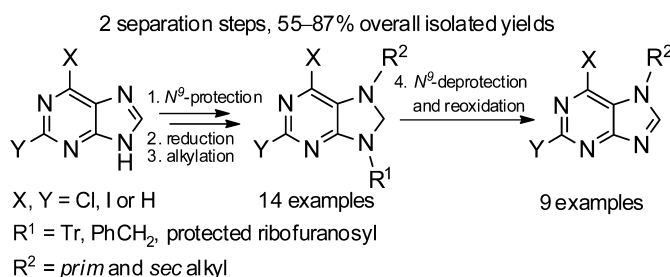
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## ABSTRACT



A simple and efficient protocol for the preparation of 7-substituted purines is described. 6- and 2,6-Dihalopurines were *N*<sup>9</sup>-tritylated and then transformed to 7,8-dihydropurines by DIBAL-H. Subsequent *N*<sup>7</sup>-alkylation followed by *N*<sup>9</sup>-trityl deprotection with trifluoroacetic acid was accompanied by spontaneous reoxidation, which led to the 7-substituted purines at 55–88% overall isolated yields.

The 2- and/or 6,9-substituted purines form a vast group of biologically active compounds.<sup>1</sup> Moreover, some naturally occurring 7-substituted purines also exhibit interesting biological properties. Caffeine represents probably the best known *N*<sup>7</sup>-substituted purine derivative. Other examples are Raphanatin and 6-(benzylamino)-7-(β-D-glucopyranosyl)purine, which possess cytokinin activity<sup>2</sup> or 2-amino-7-[(1,3-dihydroxy-2-propoxy)methyl]purine, that exhibit high anti-viral activity.<sup>3</sup> Also asmarine alkaloids with their significant cytotoxicity against various tumor cell lines can be considered as 7-substituted purines.<sup>4</sup> The other group of *N*<sup>7</sup>-substituted purines is represented by the 7,9-disubstituted

purine motif, which can be found in many biologically relevant compounds, including the mRNA cap analogs.<sup>5</sup> While the biological activity of 7-substituted purines has clearly been demonstrated, the synthetic approaches to them are rather limited in scope.

7-Substituted purines can be prepared by labored cyclization of appropriate diaminopyrimidine derivatives<sup>6</sup> or by direct alkylation of purine bases. It however, usually leads to mixtures of both *N*<sup>7</sup> and *N*<sup>9</sup>-alkyl derivatives in which the latter predominates.<sup>7</sup> Only a few 2- or 6-aminopurine derivatives have been reported to undergo *N*<sup>7</sup>-alkylation preferentially. Thus *N*<sup>3</sup>-benzyladenine can be selectively alkylated at the *N*<sup>7</sup>-position and subsequent debenzilation affords *N*<sup>7</sup>-substituted adenine.<sup>8</sup> Glycosidation of trisilylated *N*<sup>2</sup>-acetylguanine<sup>9</sup> and alkylation of disilylated 2-acetamido-6-chloropurine<sup>5</sup> was also reported to produce 7-substituted

(1) For a recent review of naturally occurring 7- and 9-substituted purines see: Rosemeyer, H. *Chem. Biodiversity* **2004**, 361.

(2) Duke, C. C.; Liepa, A. J.; MacLeod, J. K.; Letham, D. S.; Parker, C. W. *J. Chem. Soc., Chem. Commun.* **1975**, 964, and references cited therein.

(3) Jähne, G.; Kroha, H.; Müller, A.; Helsenberg, M.; Winkler, I.; Gross, G.; Scholl, T. *Angew. Chem., Int. Ed.* **1994**, 33, 562.

(4) (a) Yosief, T.; Rudi, A.; Stein, Z.; Goldberg, I.; Gravalos, G. M. D.; Schleyer, M.; Kashman, Y. *Tetrahedron Lett.* **1998**, 39, 3323. (b) Rudi, A.; Shalom, H.; Schleyer, M.; Benayahu, Y.; Kashman, Y. *J. Nat. Prod.* **2004**, 67, 106. (c) Rudi, A.; Akin, M.; Gaydou, E.; Kashman, Y. *J. Nat. Prod.* **2004**, 67, 1932. (d) Yosief, T.; Rudi, A.; Kashman, Y. *J. Nat. Prod.* **2000**, 63, 299.

(5) (a) Recent examples: Jemielity, J.; Kowalska, J.; Rydzik, A. M.; Darzynkiewicz, E. *New. J. Chem.* **2010**, 34, 829. (b) Cai, A.; Jankowska-Anyszka, M.; Centers, A.; Chebicka, L.; Stepinski, J.; Stolarski, R.; Darzynkiewicz, E.; Rhoads, R. E. *Biochemistry* **1999**, 38, 8538.

(6) Montgomery, J. A.; Hewson, K. *J. Org. Chem.* **1961**, 26, 4469.

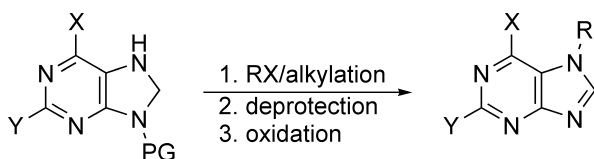
(7) (a) Montgomery, J. A.; Temple, C. *J. Am. Chem. Soc.* **1961**, 83, 630. (b) Lukin, K. A.; Yang, C.; Belletini, J. R.; Narayanan, B. A. *Nucleosides Nucleotides Nucleic Acids* **2000**, 19, 815.

purine derivatives selectively. Another example is *N*<sup>6</sup>-[(dimethylamino)methylen]adenine, which is alkylated exclusively at the *N*<sup>7</sup>-position.<sup>10</sup> We have recently shown that this compound as well as *N*<sup>2</sup>-[(dimethylamino)methylen]-guanine can also be arylated with high *N*<sup>7</sup>-selectivity.<sup>11</sup>

On the other hand, the selective *N*<sup>7</sup>-alkylation of 2- or 2,6-halopurines is a troublesome procedure, because direct alkylation leads to predominance by the *N*<sup>9</sup>-isomer.<sup>12</sup> Issues related to regioselectivity have been addressed by *N*<sup>7</sup>-alkylation of 6-chloro-9*H*-purine and 2,6-dichloro-9*H*-purines in the presence of sophisticated Co-complexes.<sup>13</sup> In addition, reversible Michael addition of 6-chloro-9*H*-purine to acrylonitrile provided a temporary *N*<sup>9</sup>-protecting group for the *N*<sup>7</sup>-alkylation of 6-chloro-9*H*-purine during the total synthesis of asmarines.<sup>14</sup> Despite some progress in the area of *N*<sup>7</sup>-alkylation of halopurines, studies of biological activity are limited by the availability of such compounds from a simple, efficient and convenient protocol.

Therefore we envisioned that selective *N*<sup>7</sup>-alkylation of 7,8-dihydropurines followed by *N*<sup>9</sup>-deprotection and reoxidation may be used as a simple route for the synthesis of *N*<sup>7</sup>-substituted purine derivatives (Scheme 1).

**Scheme 1.** Envisaged Route to 7-Alkylated-7*H*-purines



To our surprise only a few reports have been published dealing with the preparation of 7,8-dihydropurine derivatives. The reported protocols for the preparation of these compounds are limited mainly to the action of boron-derived reducing reagents, for example, NaBH<sub>4</sub>,<sup>15</sup> NaBH<sub>4</sub>/HCl,<sup>16</sup> NaBH<sub>3</sub>CN/AcOH,<sup>17</sup> BH<sub>3</sub>·THF,<sup>18</sup> and NaBH<sub>4</sub>/AcOH.<sup>19</sup> The reduction of adenine derivatives with DIBAL-H was also

mentioned.<sup>18</sup> Therefore, we initially tested the ability of the imidazolyl moiety of purine to undergo reduction under various conditions. The results are summarized in Table 1.

**Table 1.** Reduction of 9-Substituted 6-Halo and 2,6-Dihalopurines under Various Conditions

| entry | X, Y, R                                                                           | reagent <sup>a</sup>            | yield (%) <sup>b</sup>                                  |
|-------|-----------------------------------------------------------------------------------|---------------------------------|---------------------------------------------------------|
| 1     | Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ( <b>1a</b> )                | NaBH <sub>4</sub> <sup>c</sup>  | <b>2a</b> (73) <sup>d</sup> <b>1a</b> (27) <sup>d</sup> |
| 2     | Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ( <b>1a</b> )                | LiAlH <sub>4</sub>              | <b>2a</b> (77)                                          |
| 3     | Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ( <b>1a</b> )                | LiBEt <sub>3</sub> H            | <b>2a</b> (79)                                          |
| 4     | Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ( <b>1a</b> )                | LiAlH <sub>4</sub> <sup>e</sup> | <b>3a</b> (67)                                          |
| 5     | Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ( <b>1a</b> )                | DIBAL-H                         | <b>2a</b> (97)                                          |
| 6     | I, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ( <b>1b</b> )                 | DIBAL-H                         | <b>2b</b> (89)                                          |
| 7     | Cl, H, (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> C ( <b>1c</b> )              | DIBAL-H                         | <b>2c</b> (94)                                          |
| 8     | Cl, I, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ( <b>1d</b> )                | DIBAL-H                         | <b>2d</b> (97)                                          |
| 9     | MeO, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ( <b>1e</b> )               | DIBAL-H                         | <b>2e</b> (65)                                          |
| 10    | Ph, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ( <b>1f</b> )                | DIBAL-H                         | <b>2f</b> (65)                                          |
| 11    | NEt <sub>2</sub> , H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ( <b>1g</b> ) | DIBAL-H                         | –                                                       |

<sup>a</sup> Reaction conditions: Reducing reagent (1.2 equiv) was added to a solution of purines **1a–g** and the reaction mixture was stirred for 2 h at room temperature. <sup>b</sup> Isolated yield. <sup>c</sup> Reaction mixture was refluxed for 2 days. <sup>d</sup> <sup>1</sup>H NMR yield. <sup>e</sup> Reaction mixture was stirred for 4 h at 60 °C.

Attempts to use the Pd-catalyzed triethylsilane reduction<sup>20</sup> of 9-benzyl-6-chloro-9*H*-purine (**1a**) in various solvents (DMF, THF, dioxane) at an elevated temperature led to the full recovery of the starting compound. Repetition of the reported NaBH<sub>4</sub> reduction of **1a** gave **2a** at 73% <sup>1</sup>H NMR yield along with the unreacted chloropurine **1a** (Table 1, Entry 1). Complete consumption of **1a** was achieved with LiAlH<sub>4</sub> and LiBEt<sub>3</sub>H; however, the isolated yields of **2a** did not change significantly (Table 1, Entries 2,3).

Interestingly, lithium aluminum hydride reduction carried out at 60 °C furnished pyrimidine derivative **3a** (Table 1, Entry 4). In contrast, DIBAL-H selectively and efficiently reduced 6-halopurines **1a,b,c** and 2,6-dihalopurine **1d** to the corresponding 7,8-dihydropurines **2a–d** almost quantitatively (Table 1, Entries 5–8). The outcome of the reduction was considerably influenced by the nature of the substituent in position 6. While purines bearing 6-MeO (**1e**) and 6-Ph (**1f**) groups were reduced at somewhat lower yield, the 6-NEt<sub>2</sub>(**1g**) derivative failed to give any dihydropurine derivative (Table 1, Entries 9–11). The character of the substituent also influenced the stability of the obtained dihydropurine. Thus, halogen-bearing dihydropurines **2a**, **2b**, and **2d** showed excellent stability in air and no traces of reoxidized product **1** were observed after several months of storage in air in the

(8) (a) Leonard, N. J.; Fujii, T.; Saito, T. *Chem. Pharm. Bull.* **1986**, *34*, 2037. (b) Fujii, T.; Saito, T.; Inoue, I.; Kumazawa, Y.; Leonard, N. J. *Chem. Pharm. Bull.* **1986**, *34*, 1821–1825.

(9) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1988**, *53*, 1294.

(10) Hocková, D.; Buděšínský, M.; Marek, R.; Marek, J.; Holý, A. E. *J. Org. Chem.* **1999**, 2675.

(11) Keder, R.; Dvořáková, H.; Dvořák, D. *Eur. J. Org. Chem.* **2009**, 1522.

(12) For examples, see: (a) Toyota, A.; Katagiri, N.; Kaneko, C. *Chem. Pharm. Bull.* **1992**, *40*, 1039. (b) Česnek, M.; Holý, A.; Masojdková, M. *Tetrahedron* **2002**, *58*, 2985. (c) Landli, G.; Gundersen, L.-L.; Rise, F. *Tetrahedron* **1996**, *52*, 5625. (d) Brik, A.; Wu, C.-Y.; Best, M. D.; Wong, C.-H. *Bioorg. Med. Chem.* **2005**, *13*, 4622.

(13) Dalby, C.; Bleasdale, C.; Clegg, W.; Elsegood, M. R. J.; Golding, B. T.; Griffin, R. J. *Angew. Chem., Int. Ed.* **1993**, *32*, 1696.

(14) Pappo, D.; Shimony, S.; Kashman, Y. *J. Org. Chem.* **2005**, *70*, 199.

(15) Kelley, J. L.; Linn, J. A. *J. Org. Chem.* **1986**, *51*, 5435.

(16) Pendergast, W.; Hall, W. R. *J. Heterocyclic Chem.* **1989**, *26*, 1863.

(17) Sako, M.; Saito, T.; Kameyama, K.; Hirota, H.; Maki, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1298.

(18) Trafelet, H.; Stulz, E.; Leumann, C. *Helv. Chim. Acta* **2001**, *84*, 87.

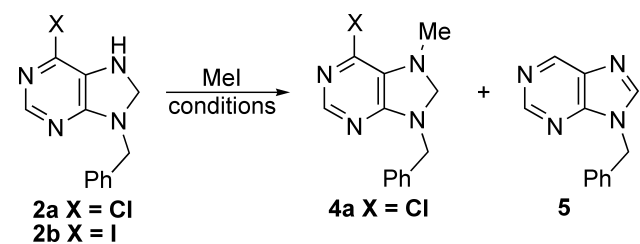
(19) Maki, Y.; Suzuki, M.; Ozeki, K. *Tetrahedron Lett.* **1976**, *17*, 1199.

(20) For recent examples of Pd-catalyzed triethylsilane reduction, see: (a) Luo, F.; Pan, C.; Wang, W.; Ye, Z.; Cheng, J. *Tetrahedron* **2010**, *66*, 1399. (b) Mandal, P. K.; McMurray, J. S. *J. Org. Chem.* **2007**, *72*, 6599. (c) Nakanishi, J.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Synlett* **2006**, 869.

solid state at room temperature. In contrast, dihydropurines containing electron-donating substituents **2e,f** and also the 9-trityl derivative **2c** were easily oxidized to **1e,f** and **1c** upon exposure to air within a couple of weeks. For their instability, the compounds **2e** and **2f** were not included in the further study.

Next, we focused on the alkylation of the obtained dihydropurines **2**. For optimization of the alkylation conditions, the reaction of **2a** and **2b** with iodomethane was carried out. The first experiments confirmed the previously reported low stability of 7,8-dihydropurines in the presence of a base.<sup>15</sup> Thus, attempts to alkylate **2a** in the presence of sodium hydride in THF afforded a 3:1 mixture of the desired 7-methylated purine **4a** and 9-benzyl-9*H*-purine (**5**) as the product of dehydrohalogenation at low yield (Table 2, Entry

**Table 2.** Optimization of the Reaction of 9-Benzyl-6-halo-7,8-dihydropurines **2** with CH<sub>3</sub>I



| entry | compound  | solvent | base, temp<br>(°C), time (h)            | yield (%) <sup>a</sup>                                 |
|-------|-----------|---------|-----------------------------------------|--------------------------------------------------------|
| 1     | <b>2a</b> | THF     | NaH, -78 to rt                          | <b>4a</b> (30) <b>5</b> (10)                           |
| 2     | <b>2a</b> | DMF     | NaH, rt, 1 <sup>b</sup>                 | <b>1a</b> (60) <sup>c</sup> <b>5</b> (21) <sup>c</sup> |
| 3     | <b>2b</b> | DMF     | NaH, rt, 1 <sup>b</sup>                 | <b>1b</b> (14) <sup>c</sup> <b>5</b> (71) <sup>c</sup> |
| 4     | <b>2a</b> | HMPA    | K <sub>2</sub> CO <sub>3</sub> , rt, 24 | <b>4a</b> (25) <b>5</b> (<10)                          |
| 5     | <b>2a</b> | HMPA    | K <sub>2</sub> CO <sub>3</sub> , 60, 20 | <b>4a</b> (15) <b>5</b> (<10)                          |
| 6     | <b>2a</b> | MeCN    | K <sub>2</sub> CO <sub>3</sub> , 60, 20 | <b>4a</b> (51) <b>5</b> (<10)                          |
| 7     | <b>2a</b> | DMF     | DBU, 0 to rt                            | <b>4a</b> (92) <sup>c</sup>                            |
| 8     | <b>2a</b> | DMF     | LiTMP, rt, 0.5                          | <b>4a</b> (88) <sup>c</sup>                            |
| 9     | <b>2a</b> | DMF     | NaH, rt, 0.5                            | <b>4a</b> (88) <sup>c</sup>                            |

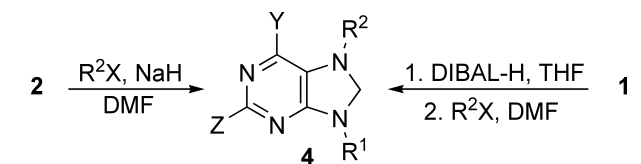
<sup>a</sup> <sup>1</sup>H NMR yield. <sup>b</sup> Reaction without CH<sub>3</sub>I. Reaction conditions: dry DMF was added to a mixture of **2a** or **2b** (1.0 equiv) and NaH (1.2 equiv). The resultant mixture without addition of CH<sub>3</sub>I was stirred for 1 h at room temperature. <sup>c</sup> Isolated yield. <sup>d</sup> Unreacted starting **2a** was recovered.

1). The tendency of **2a** and **2b** to elimination was confirmed by the reaction with NaH without CH<sub>3</sub>I. 9-Benzyl-9*H*-purine (**5**) was isolated at 21 and 71% yield, respectively, in this case (Table 2, Entries 2,3). Other bases such as K<sub>2</sub>CO<sub>3</sub> and DBU suppressed the dehydrohalogenation, but the yield of **4** did not exceed 51% (Table 2, Entries 4–7). Acceptable isolated yields of **4** were obtained when **2a** was alkylated in the presence of LiTMP or NaH in dry DMF; however, to avoid a side-reaction, DMF and iodomethane had to be mixed with a mixture of **2a** and the base simultaneously (Table 2, Entries 8,9). Since NaH is readily available and gives comparable results to lithium 2,2,6,6-tetramethylpiperidine, it was used for further alkylation experiments.

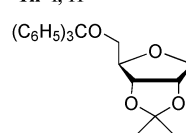
Since adenine itself and adenosine derivatives were not reduced by DIBAL-H, we focused on 6-halo and 2,6-dihalopurines as precursors of adenine and guanine derivatives. Under the above conditions 9-benzyl-6-chloro-7,8-

dihydropurine (**2a**), 6-chloro-7,8-dihydro-9-tritylpurine (**2c**) and 9-benzyl-6-chloro-7,8-dihydro-2-iodopurine (**2d**) reacted smoothly with highly reactive benzyl (Table 3, Entries 1–3),

**Table 3.** Preparation of the 7,9-Disubstituted Dihydropurines **4**



| entry | Y, Z, R <sup>1</sup>                                                          | R <sup>2</sup> X                                                    | yield (%) <sup>a,b</sup> |
|-------|-------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------|
| 1     | <b>2a</b> Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>                | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl                    | <b>4b</b> (89)           |
| 2     | <b>2a</b> Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>                | 4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Cl | <b>4c</b> (84)           |
| 3     | <b>2a</b> Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>                |                                                                     | <b>4d</b> (90)           |
| 4     | <b>2c</b> Cl, H, (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> C              | CH <sub>2</sub> =CHCH <sub>2</sub> Br                               | <b>4e</b> (95)           |
| 5     | <b>2c</b> Cl, H, (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> C              | (CH <sub>3</sub> ) <sub>2</sub> C=CHCH <sub>2</sub> Br              | <b>4f</b> (80)           |
| 6     | <b>2d</b> Cl, I, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>                | CH <sub>2</sub> =CHCH <sub>2</sub> Br                               | <b>4g</b> (84)           |
| 7     | <b>2d</b> Cl, I, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>                | (CH <sub>3</sub> ) <sub>2</sub> C=CHCH <sub>2</sub> Br              | <b>4h</b> (79)           |
| 8     | <b>2a</b> Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>                |                                                                     | <b>4i</b> (73)           |
| 9     | <b>2c</b> Cl, H, (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> C              | HC≡CCH <sub>2</sub> Br                                              | <b>4j</b> (76)           |
| 10    | <b>2d</b> Cl, I, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>                | HC≡CCH <sub>2</sub> Br                                              | <b>4k</b> (82)           |
| 11    | <b>2a</b> Cl, H, (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> C              | CH <sub>3</sub> I                                                   | <b>4l</b> (87)           |
| 12    | <b>2a</b> Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>                | C <sub>6</sub> H <sub>5</sub> OCH <sub>2</sub> CH <sub>2</sub> Br   | <b>4m</b> (99)           |
| 13    | <b>2a</b> Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>                | (CH <sub>3</sub> ) <sub>2</sub> CHI                                 | <b>4n</b> (80)           |
| 14    | <b>1a</b> <sup>c</sup> Cl, H, C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>   | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl                    | <b>4b</b> (86)           |
| 15    | <b>1c</b> <sup>c</sup> Cl, H, (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> C | CH <sub>2</sub> =CHCH <sub>2</sub> Br                               | <b>4e</b> (57)           |
| 16    | <b>1c</b> <sup>c</sup> Cl, H, (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> C | (CH <sub>3</sub> ) <sub>2</sub> C=CHCH <sub>2</sub> Br              | <b>4f</b> (70)           |
| 17    | <b>1h</b> <sup>c</sup> I, H                                                   | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl                    | <b>4o</b> (60)           |



<sup>a</sup> Isolated yield. <sup>b</sup> Reaction conditions: A solution of the alkylhalide (1.5 equiv) in dry DMF was added to a mixture of NaH (1.2 equiv) and 7,8-dihydropurine **2**. The resulting mixture was stirred for 2 h at room temperature. <sup>c</sup> “One-pot” protocol was used: DIBAL-H (1.2 equiv) was added to a solution of **1** and the mixture was stirred for 2 h at room temperature, quenched by Na<sub>2</sub>SO<sub>4</sub>·10H<sub>2</sub>O, filtrated through Celite and concentrated in vacuo. The crude product was mixed with NaH (1.2 equiv) followed by addition of a solution of RX (1.5 equiv) in dry DMF. The resulting mixture was stirred for 2 h at room temperature.

allyl (Table 3, Entries 4–8) and propargyl halides (Table 3, Entries 9,10). High yields of 7-alkylated products were also obtained with unactivated primary and secondary alkyl halides (Table 3, Entries 11–13). An attempt to simplify the above procedure by combining the reduction and alkylation steps was made. Thus, simple concentration of the reaction mixture after the reduction of **1a**, followed by the addition of NaH, dry DMF and benzyl chloride gave **4b** at 54% isolated yield. However, a different workup including quenching of the reaction mixture with Na<sub>2</sub>SO<sub>4</sub>·10H<sub>2</sub>O after reduction, filtration through Celite and concentration in vacuo followed by alkylation gave the desired **4b** at 86% yield (Table 3, Entry 14). Similarly, “one-pot” alkylation of **1c** with allyl bromide or 3,3-dimethylallyl bromide gave **4e** or **4f** at fairly good yields (Table 3, Entries 15,16). Moreover, the synthesis of *N*<sup>7</sup>-substituted-6-iodo-7,8-dihydropurine nucleoside **4o** was accomplished at 60% isolated yield using

this protocol starting from 6-iodo-9-(2,3-*O*-isopropylidene-5-*O*-trityl- $\beta$ -D-ribofuranosyl)-9H-purine (**1h**)<sup>21</sup> (Table 3, Entry 17).

The selective synthesis of 7-substituted purines was subsequently accomplished. Selection of the appropriate protecting group for the protection of position 9 of the purine ring plays a crucial role. After several attempts, the trityl group was chosen because it can be introduced with high *N*<sup>9</sup>-regioselectivity and deprotection proceeds easily under mild conditions. Thus, 6-chloro-9H-purine reacted with TrCl in the presence of triethylamine furnishing 9-trityl-6-chloro-9H-purine (**1c**) at 97% isolated yield. Subsequent reduction to **2c** (94%) followed by alkylation (Table 3, Entries 4,5,11) gave dihydropurines **4e,f,i** at 87, 73 and 79% overall yield (three steps). Subsequent deprotection by trifluoroacetic acid was accompanied by spontaneous oxidation<sup>22</sup> affording the 7-alkyl-6-chloro-9H-purines **6e**, **6f**, and **6i** at 82, 70 and 79% overall yield respectively starting from 6-chloro-9H-purine (Table 4, Entries 1–3).

In this case the overall number of separation steps can also be reduced. The starting halopurine was converted to 6-chloro-9-trityl-9H-purine (**1c**) or 2,6-dichloro-9-trityl-9H-purine (**1i**) followed by alkylation according to the above “one-pot” procedure and the crude alkylated dihydropurines **4** were directly treated with trifluoroacetic acid giving the desired 7-substituted purines **6**. Thus, benzyl, propargyl, isopropyl and (methoxycarbonyl)methyl derivatives were cleanly and selectively obtained at overall yields ranging from 55 to 86% (Table 4, Entries 4–7) using column chromatography only for the isolation of **1c** and the final 7-substituted purines **6**. Similar results were obtained for the *N*<sup>7</sup>-alkylation of 2,6-dichloropurine by 2-iodopropane and 4-methoxybenzyl bromide (Table 4, Entries 8,9).

In summary, we have developed a new simple and selective protocol for the synthesis of 7-substituted purines. This methodology is based on the successive *N*<sup>9</sup>-protection, reduction, *N*<sup>7</sup>-alkylation and *N*<sup>9</sup>-deprotection accompanied by reoxidation of the starting purine derivative. It allows the

**Table 4.** Overall Transformation of 6-Chloro- and 2,6-Dichloro-9H-purine to 7-Substituted Purines **6**

| entry | Z               | R                                                                | deprotection<br>4 → 6 (%) | overall<br>yield <sup>a</sup> (%) |
|-------|-----------------|------------------------------------------------------------------|---------------------------|-----------------------------------|
| 1     | H               | CH <sub>2</sub> =CHCH <sub>2</sub>                               | 95                        | <b>6e</b> (82)                    |
| 2     | H               | (CH <sub>3</sub> ) <sub>2</sub> C=CHCH <sub>2</sub>              | 96                        | <b>6f</b> (70)                    |
| 3     | H               | Me                                                               | 99                        | <b>6i</b> (79)                    |
| 4     | H               | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>                    | —                         | <b>6b</b> (86)                    |
| 5     | H               | HC≡CCH <sub>2</sub>                                              | —                         | <b>6j</b> (55) <sup>b</sup>       |
| 6     | H               | (CH <sub>3</sub> ) <sub>2</sub> CH                               | —                         | <b>6n</b> (73)                    |
| 7     | H               | MeO <sub>2</sub> CCH <sub>2</sub>                                | —                         | <b>6p</b> (72)                    |
| 8     | Cl <sup>c</sup> | (CH <sub>3</sub> ) <sub>2</sub> CH                               | —                         | <b>6q</b> (80)                    |
| 9     | Cl              | 4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> | —                         | <b>6r</b> (87)                    |

<sup>a</sup> Overall isolated yield starting from 6-chloro-9H-purine or 2,6-dichloro-9H-purine. <sup>b</sup> MnO<sub>2</sub> had to be used to oxidize the 6-chloro-7-propargyl-7,8-dihydropurine **4j** to **6j** quantitatively. <sup>c</sup> 2,6-Dichloro-9-trityl-9H-purine was obtained at 89% yield.

preparation of 6-halo and 2,6-dihalopurines bearing *prim.* or *sec.* alkyl, benzyl, allyl and propargyl groups in the position *N*<sup>7</sup> at 55–88% overall yield starting from the corresponding halopurine. Further studies to extend the scope of this methodology, screening of biological activity and study of the reactivity of novel 7,8-dihydropurines and 7-substituted purines are underway in our laboratory.

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**Supporting Information Available:** Experimental details and characterization data for the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(22) The oxidation of dihydropurine derivatives **4** to the purines **6** was practically quantitative in all described cases. Only in the preparation of 7-propargyl derivative **6j** was a mixture of dihydropurines **4j** and **6j** obtained. The oxidation of the above mixture was easily achieved by stirring the CH<sub>2</sub>Cl<sub>2</sub> solution with MnO<sub>2</sub> for 1 h (see Supporting information).