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

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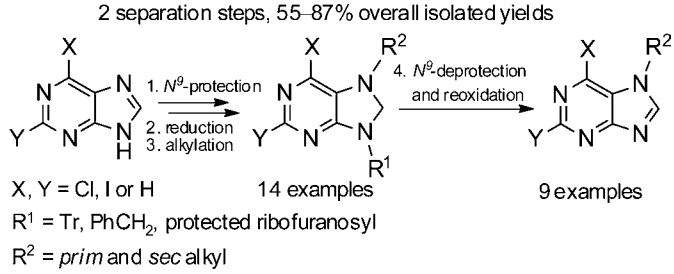
ABSTRACT



A simple and efficient protocol for the preparation of 7-substituted purines is described. 6- and 2,6-Dihalopurines were N^9-tritylated and then transformed to 7,8-dihydropurines by DIBAL-H. Subsequent N^7-alkylation followed by N^9-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.[1] Moreover, some naturally occurring 7-substituted purines also exhibit interesting biological properties. Caffeine represents probably the best known N^7-substituted purine derivative. Other examples are Raphanatin and 6-(benzylamino)-7-(β-D-glucopyranosyl)purine, which possess cytokinin activity[2] or 2-amino-7-[(1,3-dihydroxy-2-propoxy)methyl]purine, that exhibit high antiviral activity.[3] Also asmarine alkaloids with their significant cytotoxicity against various tumor cell lines can be considered as 7-substituted purines.[4] The other group of N^7-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.[5] 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[6] or by direct alkylation of purine bases. It however, usually leads to mixtures of both N^7 and N^9-alkyl derivatives in which the latter predominates.[7] Only a few 2- or 6-aminopurine derivatives have been reported to undergo N^7-alkylation preferentially. Thus N^3-benzyladenine can be selectively alkylated at the N^7-position and subsequent debenzylation affords N^7-substituted adenine.[8] Glycosidation of trisilylated N^2-acetylguanine[9] and alkylation of disilylated 2-acetamido-6-chloropurine[5] was also reported to produce 7-substituted

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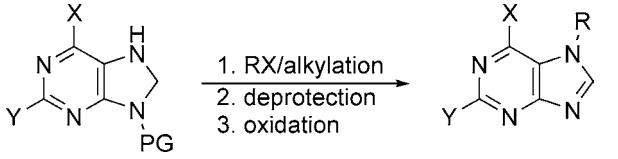
purine derivatives selectively. Another example is N^6-[(dimethylamino)methylen]adenine, which is alkylated exclusively at the N^7-position.[10] We have recently shown that this compound as well as N^2-[(dimethylamino)methylen]-guanine can also be arylated with high N^7-selectivity.[11]

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

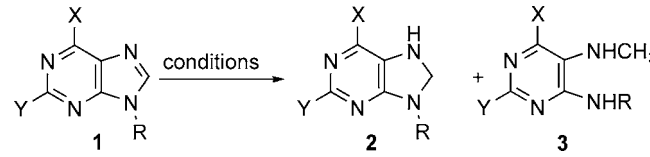
Therefore we envisioned that selective N^7-alkylation of 7,8-dihydropurines followed by N^9-deprotection and reoxidation may be used as a simple route for the synthesis of N^7-substituted purine derivatives (Scheme 1).

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, $NaBH_4$,[15] $NaBH_4$/HCl,[16] $NaBH_3CN$/AcOH,[17] BH_3·THF,[18] and $NaBH_4$/AcOH.[19] The reduction of adenine derivatives with DIBAL-H was also mentioned.[18] Therefore, we initially tested the ability of the imidazoyl 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[a]	yield (%)[b]
1	Cl, H, $C_6H_5CH_2$(**1a**)	$NaBH_4$[c]	**2a** (73)[d] **1a** (27)[d]
2	Cl, H, $C_6H_5CH_2$ (**1a**)	$LiAlH_4$	**2a** (77)
3	Cl, H, $C_6H_5CH_2$ (**1a**)	$LiBEt_3H$	**2a** (79)
4	Cl, H, $C_6H_5CH_2$ (**1a**)	$LiAlH_4$[e]	**3a** (67)
5	Cl, H, $C_6H_5CH_2$ (**1a**)	DIBAL-H	**2a** (97)
6	I, H, $C_6H_5CH_2$ (**1b**)	DIBAL-H	**2b** (89)
7	Cl, H, $(C_6H_5)_3C$ (**1c**)	DIBAL-H	**2c** (94)
8	Cl, I, $C_6H_5CH_2$ (**1d**)	DIBAL-H	**2d** (97)
9	MeO, H, $C_6H_5CH_2$ (**1e**)	DIBAL-H	**2e** (65)
10	Ph, H, $C_6H_5CH_2$ (**1f**)	DIBAL-H	**2f** (65)
11	NEt_2, H, $C_6H_5CH_2$ (**1g**)	DIBAL-H	–

[a] 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. [b] Isolated yield. [c] Reaction mixture was refluxed for 2 days. [d] ^{1}H NMR yield. [e] Reaction mixture was stirred for 4 h at 60 °C.

Attempts to use the Pd-catalyzed triethylsilane reduction[20] 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 $NaBH_4$ reduction of **1a** gave **2a** at 73% ^{1}H NMR yield along with the unreacted chloropurine **1a** (Table 1, Entry 1). Complete consumption of **1a** was achieved with $LiAlH_4$ and $LiBEt_3H$; 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_2(**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

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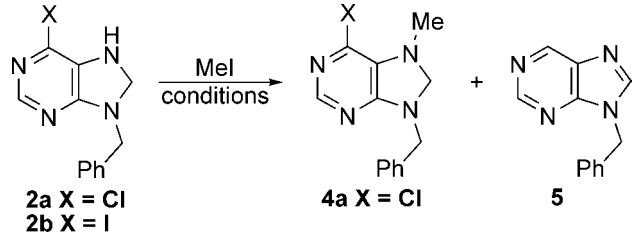
solid state at room temperature. In contrast, dihydropurines containing electron-donating substituents **2e**,**f** and also the 9-trityl derivative **2c** were easily oxidized to **1e**,**f** and **1c** upon exposure to air within a couple of weeks. For their instability, the compounds **2e** and **2f** 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.[15] 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 1). The tendency of **2a** and **2b** to elimination was confirmed by the reaction with NaH without CH_3I. 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_2CO_3 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.

Table 2. Optimization of the Reaction of 9-Benzyl-6-halo-7,8-dihydropurines **2** with CH_3I



2a X = Cl
2b X = I

4a X = Cl

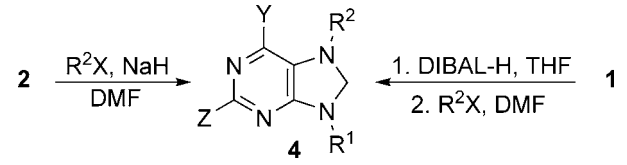
5

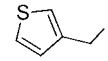
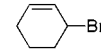
entry	compound	solvent	base, temp (°C), time (h)	yield (%)[a]
1	**2a**	THF	NaH, −78 to rt	**4a** (30) **5** (10)
2	**2a**	DMF	NaH, rt, 1[b]	**1a** (60)[c] **5** (21)[c]
3	**2b**	DMF	NaH, rt, 1[b]	**1b** (14)[c] **5** (71)[c]
4	**2a**	HMPA	K_2CO_3, rt, 24	[d]
5	**2a**	HMPA	K_2CO_3, 60, 20	**4a** (25) **5** (<10)
6	**2a**	MeCN	K_2CO_3, 60, 20	**4a** (15) **5** (<10)
7	**2a**	DMF	DBU, 0 to rt	**4a** (51) **5** (<10)
8	**2a**	DMF	LiTMP, rt, 0.5	**4a** (92)[c]
9	**2a**	DMF	NaH, rt, 0.5	**4a** (88)[c]

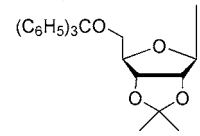
[a] ^{1}H NMR yield. [b] Reaction without CH_3I. Reaction conditions: dry DMF was added to a mixture of **2a** or **2b** (1.0 equiv) and NaH (1.2 equiv). The resultant mixture without addition of CH_3I was stirred for 1 h at room temperature. [c] Isolated yield. [d] Unreacted starting **2a** was recovered.

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), 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 $Na_2SO_4{\cdot}10H_2O$ 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^7-substituted-6-iodo-7,8-dihydropurine nucleoside **4o** was accomplished at 60% isolated yield using

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



entry	Y, Z, R^1	R^2X	yield (%)[a,b]
1	**2a** Cl, H, $C_6H_5CH_2$	$C_6H_5CH_2Cl$	**4b** (89)
2	**2a** Cl, H, $C_6H_5CH_2$	4-$CH_3OC_6H_4CH_2Cl$	**4c** (84)
3	**2a** Cl, H, $C_6H_5CH_2$		**4d** (90)
4	**2c** Cl, H, $(C_6H_5)_3C$	CH_2=$CHCH_2Br$	**4e** (95)
5	**2c** Cl, H, $(C_6H_5)_3C$	$(CH_3)_2C$=$CHCH_2Br$	**4f** (80)
6	**2d** Cl, I, $C_6H_5CH_2$	CH_2=$CHCH_2Br$	**4g** (84)
7	**2d** Cl, I, $C_6H_5CH_2$	$(CH_3)_2C$=$CHCH_2Br$	**4h** (79)
8	**2a** Cl, H, $C_6H_5CH_2$		**4i** (73)
9	**2c** Cl, H, $(C_6H_5)_3C$	$HC{\equiv}CCH_2Br$	**4j** (76)
10	**2d** Cl, I, $C_6H_5CH_2$	$HC{\equiv}CCH_2Br$	**4k** (82)
11	**2a** Cl, H, $(C_6H_5)_3C$	CH_3I	**4l** (87)
12	**2a** Cl, H, $C_6H_5CH_2$	$C_6H_5OCH_2CH_2Br$	**4m** (99)
13	**2a** Cl, H, $C_6H_5CH_2$	$(CH_3)_2CHI$	**4n** (80)
14	**1a**[c] Cl, H, $C_6H_5CH_2$	$C_6H_5CH_2Cl$	**4b** (86)
15	**1c**[c] Cl, H, $(C_6H_5)_3C$	CH_2=$CHCH_2Br$	**4e** (57)
16	**1c**[c] Cl, H, $(C_6H_5)_3C$	$(CH_3)_2C$=$CHCH_2Br$	**4f** (70)
17	**1h**[c] I, H	$C_6H_5CH_2Cl$	**4o** (60)



[a] Isolated yield. [b] 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. [c] "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 $Na_2SO_4{\cdot}10H_2O$, 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.

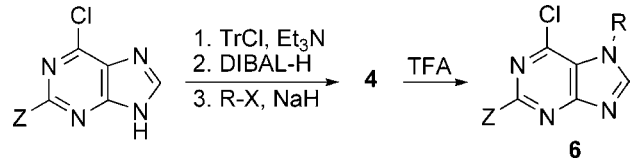
this protocol starting from 6-iodo-9-(2,3-*O*-isopropylidene-5-*O*-trityl-*β*-D-ribofuranosyl)-9*H*-purine (**1h**)[21] (Table 3, Entry 17).

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^9-regioselectivity and deprotection proceeds easily under mild conditions. Thus, 6-chloro-9*H*-purine reacted with TrCl in the presence of triethylamine furnishing 9-trityl-6-chloro-9*H*-purine (**1c**) at 97% isolated yield. Subsequent reduction to **2c** (94%) followed by alkylation (Table 3, Entries 4,5,11) gave dihydropurines **4e**,**f**,**l** at 87, 73 and 79% overall yield (three steps). Subsequent deprotection by trifluoroacetic acid was accompanied by spontaneous oxidation[22] affording the 7-alkyl-6-chloro-9*H*-purines **6e**, **6f**, and **6l** at 82, 70 and 79% overall yield respectively starting from 6-chloro-9*H*-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-9*H*-purine (**1c**) or 2,6-dichloro-9-trityl-9*H*-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^7-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^9-protection, reduction, N^7-alkylation and N^9-deprotection accompanied by reoxidation of the starting purine derivative. It allows the preparation of 6-halo and 2,6-dihalopurines bearing *prim.* or *sec.* alkyl, benzyl, allyl and propargyl groups in the position N^7 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.

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



entry	Z	R	deprotection 4 → 6 (%)	overall yield[a] (%)
1	H	CH_2=$CHCH_2$	95	**6e** (82)
2	H	$(CH_3)_2C$=$CHCH_2$	96	**6f** (70)
3	H	Me	99	**6l** (79)
4	H	$C_6H_5CH_2$	–	**6b** (86)
5	H	HC≡CCH_2	–	**6j** (55)[b]
6	H	$(CH_3)_2CH$	–	**6n** (73)
7	H	MeO_2CCH_2	–	**6p** (72)
8	Cl[c]	$(CH_3)_2CH$	–	**6q** (80)
9	Cl	4-$CH_3OC_6H_4CH_2$	–	**6r** (87)

[a] Overall isolated yield starting from 6-chloro-9*H*-purine or 2,6-dichloro-9*H*-purine. [b] MnO_2 had to be used to oxidize the 6-chloro-7-propargyl-7,8-dihydropurine **4j** to **6j** quantitatively. [c] 2,6-Dichloro-9-trityl-9*H*-purine was obtained at 89% yield.

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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_2Cl_2 solution with MnO_2 for 1 h (see Supporting information).