Highly Efficient and Broad-Scope Protocol for the Preparation of 7-Substituted 6-Halopurines via N^9-Boc-Protected 7,8-Dihydropurines

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Received 26 October 2011; revised 2 December 2011

Abstract: 9-Boc-6-chloropurine, which can be obtained in high yield, is nearly quantitatively reduced with the THF·BH_3 complex. The obtained 9-Boc-7,8-dihydropurine derivative is more stable compared to the corresponding 9-tritylpurine and can be smoothly N^7-alkylated, acylated, or it can serve as an N-nucleophile in conjugate additions. Deprotection with trifluoroacetic acid followed by MnO_2 oxidation affords the N^7-substituted purines in high yields. The whole sequence of alkylation, deprotection, and oxidation can be done with crude intermediates using chromatography only for the purification of the final N^7-substituted purine.

Key words: alkylation, acylation, Michael addition, nucleobases, reduction

Due to the wide occurrence of purine scaffolds in biological systems, many substituted purines are biologically active compounds. A vast number of purine derivatives have therefore been synthesised, and a number of them have been found to be biologically active.[1] Many synthetic methodologies, including C–C cross coupling reactions at the 2-, 6- and 8-positions, substitution of halogens by nucleophiles or N^9-alkylation, and arylation have been developed for the synthesis of purine derivatives.[2]

However, a simple and reliable methodology for the synthesis of N^7-substituted purines, despite their reported biological activity,[3] was absent until very recently. Direct alkylation of purine bases usually leads to the formation of both N^7 and N^9 isomers of which, with the exception of a few 2- and 6-aminopurines,[4] the latter predominates. Thus, N^7-substituted purines were mostly prepared by laboured cyclisation of diaminopyrimidine derivatives.[5] A more convenient method has been recently described involving cyclisation of N-substituted 5-amido-4-iodo-6-benzylsulfanylpyrimidines, which is based on copper-catalysed amidation.[6] Additionally, methodology using Co-complexes of chloropurines[7] and temporary protection of the N^9-position by reversible Michael addition of acrylonitrile in the synthesis of asmarines[8] have also been used for the N^7-alkylation of purines. Solvent dependent, preferential N^7-arylation was also observed in the arylation of N^2-[(dimethylamino)methylene]guanine and N^6-[(dimethylamino)methylene]adenine.[9]

Recently, as a part of our ongoing project to develop a new selective synthesis of C- and N^7-substituted purines,[9,10] we have developed a new practical route to the synthesis of N^7-alkyl-6-halo and N^7-alkyl-2,6-dihalopurines based on the reaction of 9-tritylated-7,8-dihydropurines with alkyl halide in the presence of a base.[11] One complication of the reported procedure is that the solutions of 9-benzyl-6-chloro-7,8-dihydropurine and 6-chloro-9-trityl-7,8-dihydropurine turned out to be prone to spontaneous oxidation to the corresponding purines in the presence of air. Since the 7,8-dihydropurines bearing electron-withdrawing substituents at the 2-, 6-, or 8-positions were reported to be more stable to oxidation,[12] we envisioned that the introduction of an electron-withdrawing group to the N^9-position of 7,8-dihydropurines could lower the electron density and thus increase the overall stability of 7,8-dihydropurines to the oxidation as well.

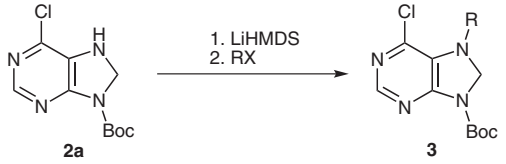
Therefore, the Boc protecting group was chosen; this can be quantitatively introduced at the N^9-position and is easily cleaved under acidic conditions. Thus, following literature procedures,[13] 6-chloro-9*H*-purine and 6-iodo-9*H*-purine were converted into the 9-*tert*-butoxycarbonyl-6-chloro-9*H*-purine (**1a**) and 9-*tert*-butoxycarbonyl-6-iodo-9*H*-purine (**1b**) by reaction with Boc_2O in the presence of triethylamine in 92% isolated yield. Contrary to the above discussed benzyl and trityl derivatives, DIBAL-H failed to reduce **1a**,**b**. From other reported reagents suitable for the preparation of 7,8-dihydropurines, the THF·BH_3 or DMS·BH_3 complex turned out to be the reagent of choice, giving 7,8-dihydropurines **2a**,**b** in quantitative isolated yield. Thus, dihydropurines **2a**,**b** can be obtained accordingly in 92% isolated yield in two steps starting from 6-chloro or 6-iodopurine. Since the previous study[11] revealed that the reactivity of 6-iodopurines was very similar to that of 6-chloro derivatives, the easier accessible 6-chloro derivative **2a** was used in the reactions mentioned here.[14]

The ability of **2a** to undergo spontaneous oxidation in solution was also tested. A solution of **2a** in anhydrous DMSO-d_6 was kept in an air atmosphere for a prolonged period of time. ^{1}H NMR analysis showed no conversion of **2a** into **1a** within 32 days. In contrast, a solution of 6-chloro-9-benzyl-7,8-dihydropurine in DMSO-d_6 was converted into 9-benzyl-6-chloropurine quantitatively during the same period of time. Prolonged storage of the above solution of **2a** did not show substantial progress of oxidation, and a 95:5 ratio of **2a**:**1a** was observed after four months.

Deprotonation of **2a** was advantageously accomplished by LiHMDS in a mixture of THF and DMF at –78 °C.[15]

SYNTHESIS 2012, 44, 610–618
Advanced online publication: 03.01.2012
DOI: 10.1055/s-0031-1290068; Art ID: Z101411SS

Addition of an alkylating agent and warming the resulting mixture to room temperature led to the formation of the N^7-alkylated product **3** in high yield (Scheme 1, Table 1). This showed a lower tendency of deprotonated **2a** to dehydrohalogenation compared to the trityl and benzyl derivatives, where simultaneous addition of the base and the alkylating agent had to be used to suppress dehydrohalogenation.[11,16] Thus, methyl iodide, propyl iodide, and benzyl bromide gave excellent yields of the alkylated products (Table 1, entries 1–3). Also, allyl bromide and the troublesome propargyl bromide[11] reacted smoothly under the above conditions (entries 4, 5). Secondary alkyls could also be smoothly introduced, which was demonstrated by the example of the isopropyl group. In this case, the isopropyl triflate gave a noticeably better result compared to the isopropyl iodide (entries 6, 7). Moreover, ester functionality was introduced by the reaction of **2a** with methyl bromoacetate and methyl 2-bromopropionate (entries 8, 9). Phenacyl bromide turned out to be a sensitive substrate under these reaction conditions, and transmetalation to zinc had to be performed before the addition of phenacyl bromide (entry 10). Alkylation reaction conditions do not tolerate a free hydroxy group. However, alkylation with TMS protected 3-iodopropan-1-ol was easy, furnishing the unprotected alcohol **3j** (as the result of acidic deprotection in situ) in 65% isolated yield (entry 11). In this case, the dihydropurine **3j** showed low stability and substantial decomposition within a couple of days upon standing at room temperature.



Scheme 1 Alkylation of 9-*tert*-butoxycarbonyl-6-chloro-7,8-dihydropurine (**2a**)

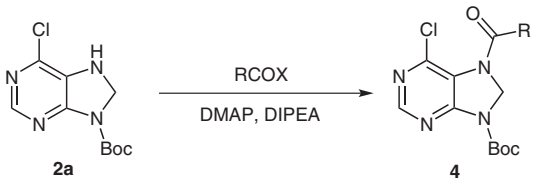
With the purpose of protecting the N^7-position for further potential synthetic transformations, acylation of the dihydropurine **2a** was also performed (Scheme 2, Table 2). Thus, the reaction of **2a** with acetic anhydride in the presence of DMAP gave the 7-acetylated product **4a** in 97% yield (Table 2, entry 1). Also, acetic acid in the presence of *N*,*N*-diisopropylcarbodiimide (DIC) and diisopropylethylamine (DIPEA) could be used for acetylation. This reaction was relatively slow and required 20% DMAP to be completed within 24 hours (entry 2). For the introduction of other acyl groups, the reaction with acyl chlorides in the presence of DMAP and DIPEA was used. The reaction proceeded smoothly with pivaloyl chloride and anisoyl chloride, while 2,2,2-trichloroethyl chloroformate reacted slower and the reaction with tosyl chloride required 24 hours to reach completion (entries 3–6). The yields, however, were excellent in all cases.

Michael addition, which in principle enables the introduction of various functionalised alkyl chains bearing electron-withdrawing groups at the β-position, was addressed next (Scheme 3). Initial screening of the reactivity of **2a** with methyl acrylate in the presence of LiHMDS failed to give any isolable amount of **5a** and decomposition of the starting compound **2a** was observed. A similar reactivity pattern, involving decomposition of the starting dihydropurine **2a**, was also observed when NaH or K_2CO_3 was used as the base (Table 3, entries 1–3). Triethylamine did not give any expected product and the unreacted starting compound was detected in the reaction mixture (entry 4). However, when 1.2 equivalents of DBU in anhydrous DMF at room temperature was used, **2a** was readily converted into **5a** within two hours in 92% isolated yield (Table 3, entry 5). Surprisingly, this reaction required more than one equivalent of DBU. With 0.1 equivalent of DBU, the reaction proceeded incompletely (entry 6). The reactions became catalytic when DMF was replaced with acetonitrile, giving 97% isolated yield of **5a** using 0.1 equivalent of DBU (entry 7). In contrast, only 65% con-

Table 1 Alkylation of 9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydropurine (**2a**) with Alkyl Halides[a]

Entry	RX	Product	Yield (%)[b]
1	MeI	**3a**	91
2	$MeCH_2CH_2I$	**3b**	84
3	$PhCH_2Br$	**3c**	91
4	CH_2=$CHCH_2Br$	**3d**	91
5	HC≡CCH_2Br	**3e**	91
6	Me_2CHI	**3f**	53
7	Me_2CHOTf	**3f**	88
8	$MeCO_2CCH_2Br$	**3g**	90
9	$MeCO_2CH(Br)Me$	**3h**	84
10	$PhCOCH_2Br$[c]	**3i**	87
11	$TMSOCH_2CH_2CH_2I$	**3j**[d,e]	65

[a] Reaction conditions: LiHMDS (1.05 equiv, 1 M solution in THF) was added to a solution of dihydropurine **2a** (1.0 equiv) in anhyd DMF (4 mL/mmol) and THF (1.3 mL/mmol) at –78 °C. The resulting mixture was stirred for 1 min at –78 °C, followed by the addition of alkyl halide (1.5 equiv). The mixture was then stirred for 20 min at r.t.
[b] Isolated yields.
[c] Li to Zn transmetalation was performed before phenacyl bromide was added.
[d] Compound partially decomposed upon standing at r.t. within a couple of days.
[e] After acidic deprotection.



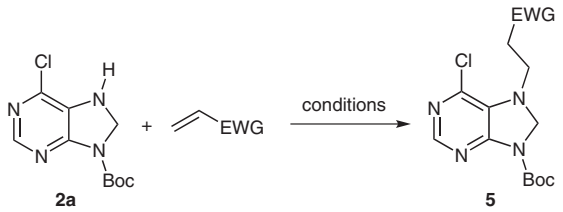
Scheme 2 Acylation of 6-chloro-7,8-dihydropurine **2a**

Table 2 Preparation of N^7-Acyl-6-chloro-7,8-dihydropurines[a]

Entry	RCOX	Time (h)	Product	Yield (%)[b]
1	Ac_2O	2	**4a**	97
2	AcOH, DIC, DMAP[c]	24	**4a**	92
3	*t*-BuCOCl	2	**4b**	97
4	4-$MeOC_6H_4COCl$	10	**4c**	96
5	Cl_3CCH_2OCOCl	15	**4d**	95
6	4-$MeC_6H_4SO_2Cl$	24	**4e**	95

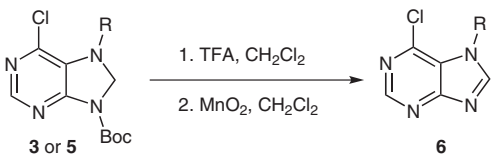
[a] Reaction conditions: acyl halide or anhydride (2 equiv) was added to a solution of 7,8-dihydropurine **2a** (1.0 equiv), DMAP (10 mol%), and DIPEA (3 equiv) in anhyd CH_2Cl_2 (5 mL/mmol) cooled to 0 °C. The resultant mixture was stirred at r.t.
[b] Isolated yields.
[c] Reaction conditions: to the suspension of **2a** and DMAP (25 mol%) in anhyd CH_2Cl_2 (5 mL/mmol) cooled to 0 °C were added AcOH (1.5 equiv) and DIC (1.5 equiv). The resultant mixture was stirred at r.t.

version was observed in THF (entry 8). This phenomenon can be explained by the change of relative pK_a values of the reagents in different solvents. Similar results as with methyl acrylate in acetonitrile were obtained using acrylonitrile as the Michael acceptor. Also, but-3-en-2-one reacted catalytically and smoothly in acetonitrile (entries 9, 10). In contrast, with acrolein, a complex reaction mixture was formed in which the expected product was not observed (Table 3, entry 11).



Scheme 3 Reaction of Michael acceptors with **2a**

Finally, the conversion of representative examples of the 7-substituted 9-Boc-dihydropurine derivatives **3** and **5** into the corresponding 7-substituted purines **6** was accomplished (Scheme 4). The Boc-protective group was smoothly removed by treatment with trifluoroacetic acid in dichloromethane and the obtained N^7-substituted purine was then, without purification, oxidised by MnO_2 in the same solvent. The summarised results in Table 4 show uniformly high overall yields after both the deprotection and oxidation steps. Thus, substituents bearing alkynyl,



Scheme 4 Preparation of 7-substituted 6-chloropurines **6**

Table 3 Reaction of Michael Acceptors with **2a** in the Presence of a Base[a]

Entry	Alkene	Base (amount)	Solvent	Product (Yield, %)[b]
1	CH_2=$CHCO_2Me$	LiHMDS	DMF–THF	–[c]
2	CH_2=$CHCO_2Me$	NaH	DMF	–[c]
3	CH_2=$CHCO_2Me$	K_2CO_3	DMF	–[c]
4	CH_2=$CHCO_2Me$	Et_3N	DMSO	–[d]
5	CH_2=$CHCO_2Me$	DBU (1.2 equiv)	DMF	**5a** (92)
6	CH_2=$CHCO_2Me$	DBU (0.1 equiv)	DMF	**5a**[e]
7	CH_2=$CHCO_2Me$	DBU (0.1 equiv)	MeCN	**5a** (97)
8	CH_2=$CHCO_2Me$	DBU (0.1 equiv)	THF	**5a**[e]
9	CH_2=CHCN	DBU (0.1 equiv)	MeCN	**5b** (97)
10	CH_2=CHCOMe	DBU (0.1 equiv)	MeCN	**5c** (95)
11	CH_2=CHCHO	DBU (0.1 equiv)	MeCN	–[f]

[a] Reaction conditions: alkene (2.0 equiv) and the base were added to a solution of 7,8-dihydropurine (1.0 equiv) in an anhyd solvent (4 mL/mmol), and the reaction mixture was stirred for 2 h at r.t.
[b] Isolated yields.
[c] Decomposition of **2a** was observed.
[d] No reaction was observed.
[e] Incomplete conversion of **2a** into **5a** was noted even at elevated temperature.
[f] Complex mixture was formed.

ester, ketone, and nitrile functionality were introduced to position 7 in high yields starting from 7,9-disubstituted 7,8-dihydropurines **3a**, **3c**, **3d**, **3e**, and **5a–c**. In the case of the derivatives **6b**, **6e**, and **6g**, a three-step procedure starting from **2a** including alkylation, deprotection and reoxidation with chromatographic purification of the final product **6** was also performed. Thus, 7-alkylated purines **6b**, **6e**, and **6g** were isolated in 81, 75, and 92% yield, respectively (Table 4, entries 2, 5, and 6).

In summary, we have demonstrated that a Boc protecting group is suitable for the synthesis of 7-substituted purines via 7,8-dihydropurines. Compared to the earlier reported 9-trityl derivatives, the 9-Boc-7,8-dihydropurines are less prone to the oxidation and therefore significantly expand the synthetic possibilities of 7,8-dihydropurines. Thus, 6-chloro-9-Boc-9*H*-purine is reduced quantitatively with $THF{\cdot}BH_3$ in anhydrous THF. The obtained 7,8-dihydropurine derivative is more stable compared to the corresponding trityl and benzyl derivatives and can be readily alkylated, acylated, or it can serve as an N-nucleophile in conjugate additions. The 7-substituted purines can then be easily obtained by Boc-deprotection with trifluoroacetic acid followed by MnO_2 oxidation in overall yields ranging from 79–89%. Moreover, the described protocol can be further simplified, and it is possible to perform alkylation or Michael addition followed by deprotection and oxidation on the crude isolated intermediates using chromatography only for the isolation of the final 7-substituted 6-

Table 4 Preparation of 7-Substituted 6-Chloropurines **6**

Entry	Starting material	R	Product (yield, %)[a,b]	Yield (%) starting from **2a**[c]
1	**3a**	Me	**6a** (92)	84
2	**3c**	CH_2Ph	**6b** (94)	86, (81)[d]
3	**3d**	$CH_2CH{=}CH_2$	**6c** (93)	85, (90)[d]
4	**3e**	$CH_2C{\equiv}CH$	**6d** (91)	83
5	**5a**	$CH_2CH_2CO_2Me$	**6e** (97)	89 (93)[d]
6	**5b**	CH_2CH_2CN	**6f** (87)	79
7	**5c**	CH_2CH_2COMe	**6g** (91)	79 (92)[d]

[a] Reaction conditions: N^7-substituted dihydropurine **3** or **5** (1.0 equiv) was added to a solution of trifluoroacetic acid (1 mL/mmol) in anhyd CH_2Cl_2 (1 mL/mmol). The mixture was stirred for 90 min at r.t., and after workup (see experimental), the crude isolated product was mixed with MnO_2 (5.0 equiv) and CH_2Cl_2 (5 mL/mmol) and stirred for 1 h at r.t.

[b] Isolated yield starting from pure **3** or **5** after two steps.

[c] Overall isolated yield starting from **2a** after three steps with isolation of the intermediate **3** or **5**.

[d] Overall isolated yield starting from **2a** after three steps using column chromatography only for the isolation of final product **6**.

chloro-7*H*-purines. Further studies on the reactivity of 7,8-dihydropurines and their applications in the synthesis of novel purine derivatives are ongoing in our laboratory.

All reactions were performed under an argon atmosphere. NMR spectra were measured on a Varian Gemini 300 (^{1}H, 300.07 MHz; ^{13}C, 75.46 MHz) spectrometer at 298 K. IR spectra were recorded on Nicolet 6700 with continuum microscope. High-resolution mass spectra were recorded on LTQ Orbitrap Velos spectrometer (Thermo Scientific). The solvents were dried and degassed by standard procedures; silica gel (Merck, Silica Gel 60, 40–63 μm) was used for column chromatography. 9-*tert*-Butoxycarbonyl-6-chloro-9*H*-purine (**1a**),[13] isopropyl triflate,[17] and 1-[(trimethylsilyl)oxy]-3-iodopropane[18] were prepared by the reported procedures; other compounds were purchased.

9-*tert*-Butoxycarbonyl-6-iodo-9*H*-purine (1b)

Anhyd THF (200 mL) was added to a mixture of 6-iodo-9*H*-purine (24.6 g, 0.1 mol) and Boc_2O (22.9 g, 0.105 mol). The mixture was vigorously stirred followed by the addition of Et_3N (10 mL, 0.072 mol). Then the mixture was stirred 1 h at r.t., concentrated in vacuo, dissolved in CH_2Cl_2 (80 mL), and filtered (hexane–EtOAc, 1:2) through silica gel (200 g). Subsequent crystallisation from hexane–EtOAc (1:2) gave the title compound as a white solid; yield: 31.9 g (92%); mp >110 °C (dec.).

IR (ATR): 3119, 3010, 2975, 2933, 1785, 1759, 1581, 1550, 1488, 1436, 1374, 1344, 1330, 1293, 1258, 1218, 1203, 1163, 1088, 913, 838, 821, 764 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 [s, 9 H, $C(CH_3)_3$], 8.55 (s, 1 H, Pu-H), 8.77 (s, 1 H, Pu-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1, 88.2, 123.1, 139.5, 143.4, 145.8, 147.6, 154.1.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{11}IN_4O_2$: 345.9927; found: 345.9924.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydropurine (2a)

THF·BH_3 (110 mL, 0.11 mol, 1 M solution in THF) was added to a solution of **1a** (25.5 g, 0.10 mol) in anhyd THF (300 mL) cooled to –78 °C. Then, the mixture was warmed to 0 °C, stirred 30 min, diluted with CH_2Cl_2 (500 mL), quenched by the addition of aq NH_4Cl (500 mL), and extracted with CH_2Cl_2 (2 × 500 mL). Collected organic layers were dried (Na_2SO_4), concentrated in vacuo, and the isolated crude product was filtered through silica gel (300 g) using EtOAc–CH_2Cl_2 (1:3) mixture. The solvents were evaporated in vacuo and the title compound was isolated as a white solid; yield: 25.3 g (99%); mp >185 °C (dec.).

IR (ATR): 3297, 2981, 2909, 1730, 1596, 1569, 1504, 1463, 1423, 1358, 1292, 1257, 1218, 1154, 1126, 1092, 1061, 907, 848, 769, 660 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 5.18 (s, 2 H, CH_2), 6.98 (br s, 1 H, NH), 7.91 (s, 1 H, H-2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.4, 65.1, 82.9, 132.0, 132.7, 147.8, 148.8, 154.8.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{13}ClN_4O_2$: 256.0727; found: 256.0724.

9-*tert*-Butoxycarbonyl-7,8-dihydro-6-iodopurine (2b)

THF·BH_3 (11 mL, 11 mmol, 1 M solution in THF) was added to a solution of **1b** (3.46 g, 0.10 mol) in anhyd THF (30 mL) cooled to –78 °C. Then the mixture was warmed to 0 °C, stirred 30 min, diluted with CH_2Cl_2 (50 mL), quenched by the addition of aq NH_4Cl (500 mL), and extracted with CH_2Cl_2 (2 × 500 mL). Collected organic layers were dried (Na_2SO_4), concentrated in vacuo, and the isolated crude product was filtered through silica gel (300 g) using EtOAc–CH_2Cl_2 (1:3) mixture. The solvents were evaporated in vacuo and the title compound was isolated as a yellow solid; 3.44 g (99%); mp >165 °C (dec.).

IR (ATR): 3238, 2979, 2902, 1732, 1593, 1564, 1456, 1392, 1367, 1307, 1287, 1257, 1207, 1152, 1126, 1058, 884, 842, 787, 766 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 [s, 9 H, $C(CH_3)_3$], 4.31 (br s, 1 H, NH), 5.31 (s, 2 H, CH_2), 8.03 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 63.6, 84.1, 99.7, 138.2, 148.8, 149.8, 151.5.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{13}IN_4O_2$: 348.0083; found: 348.0070.

Alkylation of Dihydropurine 2a; General Procedure

LiHMDS (1.05 equiv, 1 M solution in THF) was added to a solution of dihydropurine **2a** (1.0 equiv) in anhyd DMF (4 mL/mmol) and THF (1.3 mL/mmol) at –78 °C. The resultant mixture was stirred for 1 min at –78 °C, followed by the addition of alkyl halide (1.5 equiv). Then, the mixture was warmed to r.t., stirred 20 min, quenched by the addition of aq NH_4Cl (10 mL), and diluted with EtOAc (35 mL). The organic layer was separated, washed with brine (3 × 35 mL), and dried (Na_2SO_4). The solvents were evaporated in vacuo and column chromatography of the residue gave the final product.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydro-7-methylpurine (3a)

Following the general procedure, starting from **2a** (0.771 g, 3.0 mmol), LiHMDS (3.15 mL, 3.15 mmol, 1 M solution in THF), MeI (0.639 g, 4.5 mmol), anhyd DMF (12 mL), and anhyd THF (3.9 mL), the title compound was obtained after column chromatography (silica gel, hexane–EtOAc, 1:1) as a white solid; yield: 0.739 g (91%); mp 88–90 °C.

IR (ATR): 2975, 2931, 2855, 1744, 1709, 1587, 1568, 1476, 1438, 1412, 1393, 1366, 1329, 1311, 1299, 1260, 1149, 1080, 977, 888, 852, 816, 761, 727 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 [s, 9 H, $C(CH_3)_3$], 3.13 (s, 3 H, CH_3), 5.11 (s, 2 H, CH_2), 8.11 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 35.1, 70.8, 84.0, 131.2, 133.0, 148.2, 148.5, 155.2.

HRMS (EI): *m*/*z* calcd for $C_{11}H_{15}ClN_4O_2$: 270.0884; found: 270.0887.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydro-7-propylpurine (3b)

Following the general procedure, starting from **2a** (0.257 g, 1.0 mmol), LiHMDS (1.05 mL, 1.05 mmol, 1 M solution in THF), propyl iodide (0.255 g, 1.5 mmol), anhyd DMF (4 mL), and anhyd THF (1.3 mL), the title compound was obtained after column chromatography (silica gel, hexane–EtOAc, 1:1) as a colourless amorphous solid; yield: 0.251 g (84%).

IR (ATR): 2964, 2933, 2873, 1749, 1705, 1566, 1503, 1469, 1446, 1420, 1392, 1367, 1344, 1290, 1256, 1224, 1201, 1165, 1146, 1103, 1086, 988, 889, 760, 732 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.52 [s, 9 H, $C(CH_3)_3$], 1.59 (m, 2 H, CH_2), 3.40 (t, *J* = 7.4 Hz, 2 H, NCH_2), 5.11 (s, 2 H, CH_2), 8.03 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 21.5, 28.3, 49.4, 69.1, 84.0, 130.7, 132.3, 148.1, 148.3, 155.2.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{19}ClN_4O_2$: 298.1197; found: 298.1199.

9-*tert*-Butoxycarbonyl-7-benzyl-6-chloro-7,8-dihydropurine (3c)

Following the general procedure, starting from **2a** (1.29 g, 5.0 mmol), LiHMDS (5.25 mL, 5.25 mmol, 1 M solution in THF), benzyl bromide (0.941 g, 5.5 mmol), anhyd DMF (20 mL), and anhyd THF (6.5 mL), the title compound was obtained after column chromatography (silica gel, hexane–EtOAc, 1:1) as a white solid; yield: 1.574 g (91%); mp 93–95 °C.

IR (ATR): 2984, 2930, 2869, 1704, 1596, 1473, 1444, 1423, 1392, 1367, 1334, 1300, 1261, 1157, 1083, 1018, 999, 915, 887, 849, 816, 775, 761, 728, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 [s, 9 H, $C(CH_3)_3$], 4.73 (s, 2 H, CH_2), 5.04 (s, 2 H, CH_2), 7.26–7.40 (m, 5 H, C_6H_5), 8.13 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 51.5, 68.6, 84.2, 128.0, 128.4, 129.2, 130.5, 132.9, 136.1, 148.3, 148.7, 155.2.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{19}ClN_4O_2$: 346.1197; found: 246.1194.

7-Allyl-9-*tert*-butoxycarbonyl-6-chloro-7,8-dihydropurine (3d)

Following the general procedure, starting from **2a** (0.514 g, 2.0 mmol), LiHMDS (2.1 mL, 2.1 mmol, 1 M solution in THF), allyl bromide (0.363 g, 3.0 mmol), anhyd DMF (8 mL), and anhyd THF (2.6 mL), the title compound was obtained after column chromatography (silica gel, hexane–EtOAc, 1:1) as a white solid; yield: 0.543 g (91%); mp 76–80 °C.

IR (ATR): 2982, 2934, 2864, 1709, 1569, 1503, 1471, 1440, 1420, 1393, 1370, 1335, 1301, 1268, 1191, 1154, 1090, 991, 936, 912, 887, 849, 817, 763, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 [s, 9 H, $C(CH_3)_3$], 4.10 (d, *J* = 6.3 Hz, 2 H, NCH_2), 5.10 (s, 2 H, CH_2), 5.28 (d, *J* = 11.1 Hz, 1 H, =CH_2), 5.29 (d, *J* = 16.5 Hz, 1 H, =CH_2), 5.82 (m, 1 H, =CH), 8.10 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 50.2, 68.5, 84.1, 119.4, 130.2, 132.1, 133.2, 148.4, 148.8, 155.5.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{17}ClN_4O_2$: 296.1040; found: 296.1035.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydro-7-propargylpurine (3e)

Following the general procedure, starting from **2a** (0.514 g, 2.0 mmol), LiHMDS (2.1 mL, 2.1 mmol, 1 M solution in THF), propargyl bromide (0.357 g, 3.0 mmol), anhyd DMF (8 mL), and anhyd THF (2.6 mL), the title compound was obtained after column chromatography (silica gel, hexane–EtOAc, 1:1) as a white solid; yield: 0.536 g (91%); mp 92–94 °C.

IR (ATR): 3297, 3071, 2987, 2855, 1703, 1570, 1503, 1472, 1453, 1437, 1416, 1371, 1343, 1297, 1266, 1225, 1183, 1159, 1098, 1013, 920, 891, 850, 815, 764, 734, 682, 659 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 [s, 9 H, $C(CH_3)_3$], 2.28 (t, *J* = 2.4 Hz, 1 H, CH), 4.25 (d, *J* = 2.4 Hz, 2 H, NCH_2), 5.18 (s, 2 H, CH_2), 8.21 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 68.5, 74.5, 77.2, 84.2, 29.5, 136.2, 148.3, 150.5, 156.2.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{15}ClN_4O_2$: 294.0884; found: 294.0884.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydro-7-isopropylpurine (3f)

Following the general procedure, starting from **2a** (0.257 g, 1.0 mmol), LiHMDS (1.05 mL, 1.05 mmol, 1 M solution in THF), isopropyl triflate (1.5 mL of freshly prepared 1 M solution in CCl_4), anhyd DMF (4 mL), and anhyd THF (1.3 mL), the title compound was obtained after column chromatography (silica gel, hexane–EtOAc, 1:1) as a white solid; yield: 0.263 g (88%). The same procedure using isopropyl iodide (0.15 mL, 1.5 mmol) instead of isopropyl triflate afforded the same product; yield: 0.158 g (53%); mp 88–90 °C.

IR (ATR): 2981, 2970, 2933, 1710, 1564, 1474, 1445, 1415, 1393, 1368, 1322, 1294, 1271, 1249, 1211, 1152, 1032, 972, 762 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 9.9 Hz, 6 H, 2 CH_3), 1.51 [s, 9 H, $C(CH_3)_3$], 4.57 (m, 1 H, CH), 5.08 (s, 1 H, CH_2), 8.01 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 28.3, 47.0, 63.2, 84.0, 130.1, 132.8, 148.3, 148.5, 155.8.

HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{19}ClN_4O_2$ + Na: 321.10942; found: 321.10867.

Methyl (9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydropurin-7-yl)acetate (3g)

Following the general procedure, starting from **2a** (0.257 g, 1.0 mmol), LiHMDS (1.05 mL, 1.05 mmol, 1 M solution in THF), methyl bromoacetate (0.230 g, 1.5 mmol), anhyd DMF (4 mL), and anhyd THF (1.3 mL), the title compound was obtained column chromatography (silica gel, hexane–EtOAc, 1:1) as a white solid; yield: 0.296 g (90%); mp 125–129 °C.

IR (ATR): 2978, 2958, 2935, 2875, 1750, 1711, 1698, 1570, 1501, 1468, 1420, 1396, 1369, 1349, 1297, 1263, 1237, 1222, 1181, 1157, 1101, 1028, 983, 927, 891, 850, 818, 779, 766, 741, 701, 656 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 [s, 9 H, $C(CH_3)_3$], 3.76 (s, 3 H, OCH_3), 4.29 (s, 2 H, CH_2), 5.21 (s, 2 H, CH_2), 8.14 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 48.0, 52.8, 69.4, 84.2, 129.9, 133.2, 148.1, 149.3, 155.4, 167.5.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{17}ClN_4O_4$: 328.0938; found: 328.0938.

Methyl (9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydropurin-7-yl)propionate (3h)

Following the general procedure, starting from **2a** (0.257 g, 1.0 mmol), LiHMDS (1.05 mL, 1.05 mmol, 1 M solution in THF), methyl 2-bromopropionate (0.169 g, 1.5 mmol), anhyd DMF (4 mL), and anhyd THF (1.3 mL), the title compound was obtained after column chromatography (silica gel, hexane–EtOAc, 1:1) as a white solid; yield: 0.288 g (84%); mp 90–93 °C.

IR (ATR): 2982, 2958, 1738, 1709, 1564, 1500, 1456, 1418, 1392, 1369, 1334, 1297, 1263, 1221, 1196, 1155, 1111, 1065, 975, 960, 883, 847, 817, 763, 723 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.49 (m, 3 H, CHCH_3), 1.51 [s, 9 H, C(CH_3)$_3$], 3.68 (s, 3 H, OCH_3), 5.10 (q, *J* = 7.2 Hz, 1 H, C*H*CH_3), 5.18 (m, 2 H, CH_2), 8.08 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 28.2, 53.0, 54.1, 65.9, 84.1, 130.1, 133.9, 148.1, 149.6, 155.7, 172.1.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{19}ClN_4O_4$: 342.1095; found: 342.1094.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydro-7-phenacylpurine (3i)

LiHMDS (1.05 mL, 1.05 mmol, 1 M solution in THF) was added to a solution dihydropurine **2a** (0.257 g, 1.0 mmol) in anhyd DMF (4 mL) and anhyd THF (1.3 mL) at –78 °C. The resultant mixture was stirred 1 min at –78 °C, followed by the addition of $ZnBr_2$ (1.0 mL, 1.0 mmol, 1 M solution in THF). Then, the reaction mixture was stirred 30 min at –78 °C, followed by the addition of phenacyl bromide (0.22 g, 1.1 mmol). The mixture was then warmed to r.t., stirred for 20 min, quenched with aq NH_4Cl (10 mL), and diluted with EtOAc (35 mL). The organic layer was washed with brine (3 × 35 mL) and dried (Na_2SO_4). The solvents were evaporated in vacuo and column chromatography of the residue (silica gel, hexane–EtOAc, 1:1) gave the final product as a yellow solid; yield: 0.325 g (87%); mp 159–161 °C.

IR (ATR): 2973, 2947, 1744, 1689, 1585, 1473, 1434, 1396, 1370, 1316, 1290, 1256, 1232, 1180, 1153, 1088, 1019, 986, 911, 888, 847, 832, 754, 686 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.57 [s, 9 H, C(CH_3)$_3$], 4.99 (s, 2 H, CH_2), 5.25 (s, 2 H, CH_2), 7.5–7.7 (m, 3 H, C_6H_5), 7.94 (dd, *J* = 1.5, 8.4 Hz, 2 H, C_6H_5), 8.15 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 52.7, 69.7, 84.1, 128.1, 129.3, 130.7, 132.6, 134.2, 134.5, 148.8, 149.4, 155.5, 193.9.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{19}ClN_4O_3$: 374.1146; found: 374.1132.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydro-7-(3-hydroxypropyl)purine (3j)

Following the general procedure, starting from **2a** (0.257 g, 1.0 mmol), LiHMDS (1.05 mL, 1.05 mmol, 1 M solution in THF), trimethyl(3-iodopropyloxy)silane (0.387 g, 1.5 mmol), anhyd DMF (4 mL), anhyd THF (1.3 mL), and acidic deprotection (1 M AcOH–MeOH/silica gel), the title compound was obtained after column chromatography (silica gel, hexane–EtOAc, 1:1) as a colourless oil; 0.219 g (65%).

IR (ATR): 3401, 2978, 2931, 2874, 1739, 1709, 1589, 1567, 1589, 1567, 1468, 1450, 1421, 1369, 1323, 1291, 1255, 1142, 1079, 888, 761 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 [s, 9 H, C(CH_3)$_3$], 1.80 (m, 2 H, CH_2), 3.55 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.69 (t, *J* = 6.0 Hz, 2 H, CH_2), 5.12 (s, 2 H, CH_2), 7.98 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 31.0, 45.1, 59.7, 69.3, 84.2, 130.7, 132.2, 148.1, 148.2, 155.4.

HRMS (ES): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{19}ClN_4O_3$ + Na: 337.10435; found: 337.10324.

Acylation of 7,8-Dihydropurine 2a; General Procedure

Acyl halide (2.0 equiv) was added to a solution of 7,8-dihydropurine **2a** (1.0 equiv), DMAP (10 mol%), DIPEA (3 equiv) in anhyd CH_2Cl_2 (5 mL/mmol) cooled to 0 °C. The resultant mixture was stirred at r.t. and concentrated in vacuo. The product was purified by column chromatography.

7-Acetyl-9-*tert*-butoxycarbonyl-6-chloro-7,8-dihydropurine (4a)

Following the general procedure, a mixture of **2a** (0.257 g, 1.0 mmol), DMAP (0.012 g, 0.1 mmol), DIPEA (0.51 mL, 3.0 mmol), and Ac_2O (0.19 mL, 2.0 mmol) was stirred for 2 h at r.t. and concentrated in vacuo. Column chromatography of the residue (silica gel, hexane–EtOAc, 1:1) gave the title compound as a white solid; yield: 0.289 g (97%); mp 157–161 °C.

IR (ATR): 2984, 2930, 1745, 1695, 1586, 1563, 1468, 1416, 1384, 1372, 1306, 1256, 1215, 1199, 1155, 1138, 1090, 1037, 1006, 905, 884, 848, 813, 756, 719 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.58 [s, 9 H C(CH_3)$_3$], 2.34 (s, 3 H, CH_3), 5.56 (s, 2 H, CH_2), 8.49 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.8, 28.3, 65.6, 85.1, 123.1, 144.1, 147.6, 154.7, 157.6, 169.4.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}ClN_4O_3$: 298.0833; found; 298.0836.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydro-7-pivaloylpurine (4b)

Following the general procedure, a mixture of **2a** (0.257 g, 1.0 mmol), DMAP (0.012 g, 0.1 mmol), DIPEA (0.51 mL, 3.0 mmol), and pivaloyl chloride (0.25 mL, 2.0 mmol) was stirred for 2 h at r.t. and concentrated in vacuo. Column chromatography of the residue (silica gel, hexane–EtOAc, 1:1) gave the title compound as a white solid; yield: 0.33 g (97%); mp 141–144 °C.

IR (ATR): 2985, 1708, 1687, 1591, 1565, 1449, 1383, 1370, 1330, 1286, 1251, 1190, 1141, 1074, 1038, 894, 876, 840, 771, 749, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 [s, 9 H, C(CH_3)$_3$], 1.59 [s, 9 H, C(CH_3)$_3$], 5.57 (s, 2 H, CH_2), 8.74 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2, 28.3, 40.9, 65.5, 84.9, 125.2, 146.4, 148.1, 154.4, 156.1, 177.5.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{21}ClN_4O_3$: 340.1302; found: 340.1303.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydro-7-(4-methoxybenzoyl)purine (4c)

Following the general procedure, a mixture of **2a** (0.257 g, 1.0 mmol), DMAP (0.012 g, 0.1 mmol), DIPEA (0.51 mL, 3.0 mmol), and 4-methoxybenzoyl chloride (0.27 g, 2.0 mmol) was stirred for 15 h at r.t., and concentrated in vacuo. Column chromatography of the residue (silica gel, hexane–EtOAc, 1:1) gave the title compound as a white solid; yield: 0.371 g (95%); mp 162–165 °C.

IR (ATR): 2978, 1742, 1668, 1604, 1579, 1564, 1513, 1447, 1422, 1384, 1369, 1302, 1257, 1236, 1188, 1133, 1089, 1019, 884, 862, 843, 809, 757 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, C(CH_3)$_3$], 3.80 (s, 3 H, CH_3), 5.45 (s, 2 H, CH_2), 6.91 (d, *J* = 8.7 Hz, 2 H, ArH), 7.61 (d, *J* = 8.7 Hz, 2 H, ArH), 8.39 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 55.8, 67.5, 85.0, 114.6, 124.4, 124.8, 131.2, 145.7, 150.0, 154.7, 157.2, 163.8, 168.4.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{19}ClN_4O_4$: 390.1095; found: 390.1091.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydro-7-(2,2,2-trichloroethoxycarbonyl)purine (4d)

Following the general procedure, a mixture of **2a** (0.257 g, 1.0 mmol), DMAP (0.012 g, 0.1 mmol), DIPEA (0.51 mL, 3.0 mmol), and 2,2,2-trichloroethyl chloroformate (0.28 mL, 2.0 mmol) was stirred for 10 h at r.t., and concentrated in vacuo. Column chromatography of the residue (silica gel, hexane–EtOAc, 1:1) gave the title compound as a beige solid; 0.41 g (97%); mp 138–142 °C.

IR (ATR): 2986, 1736, 1590, 1562, 1472, 1416, 1400, 1309, 1288, 1216, 1160, 1138, 1087, 1036, 944, 887, 812, 754, 713 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.58 [s, 9 H, $C(CH_3)_3$], 4.92 (s, 2 H, CH_2), 5.59 (s, 2 H, CH_2), 8.50 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 65.5, 76.0, 85.2, 94.5, 122.4, 144.6, 147.6, 150.3, 154.8, 156.9.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{14}Cl_4N_4O_4$: 429.9769; found: 429.9756.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydro-7-(4-toluenesulfonyl)purine (4e)

Following the general procedure, a mixture of **2a** (0.257 g, 1.0 mmol), DMAP (0.012 g, 0.1 mmol), DIPEA (0.51 mL, 3.0 mmol), and 4-toluenesulfonyl chloride (0.381 g, 2.0 mmol) was stirred for 24 h at r.t., and concentrated in vacuo. Column chromatography of the residue (silica gel, hexane–EtOAc, 1:1) gave the title compound as a white solid; 0.390 g (95%); mp 154–157 °C.

IR (ATR): 2980, 2931, 1715, 1590, 1567, 1484, 1449, 1396, 1373, 1348, 1301, 1244, 1175, 1160, 1087, 1057, 1017, 975, 896, 870, 845, 817, 802, 784, 762, 708, 671 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 2.38 (s, 3 H, CH_3), 5.41 (s, 2 H, CH_2), 7.24 (d, *J* = 8.8 Hz, 2 H, ArH), 7.53 (d, *J* = 8.8 Hz, 2 H, ArH), 8.45 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 28.2, 67.1, 84.9, 123.5, 127.7, 130.3, 132.6, 146.2, 149.2, 156.3, 159.6.

HRMS: *m*/*z* calcd for $C_{17}H_{19}ClN_4O_4S$: 410.0816; found: 410.0807.

Michael Addition Reactions of 7,8-Dihydropurine 2a; General Procedure

Michael acceptor (2.0 equiv) and DBU (0.1 equiv) were added to a suspension of 7,8-dihydropurine **2a** (1.0 equiv) in anhyd MeCN (4 mL/mmol). The reaction mixture was then stirred for 2 h at r.t., concentrated in vacuo, and the product was purified by column chromatography.

Methyl 3-(9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydropurin-7-yl)propionate (5a)

Following the general procedure, starting from **2a** (1.285 g, 5.0 mmol), methyl acrylate (0.860 g, 10.0 mmol), DBU (0.912 g, 6.0 mmol), and anhyd MeCN (20 mL), the title compound was obtained after column chromatography (silica gel, hexane–EtOAc, 1:1) as a white solid; 1.593 g (97%); mp 89–92 °C.

IR (ATR): 3073, 2985, 2954, 2866, 1799, 1736, 1702, 1667, 1594, 1571, 1504, 1470, 1440, 1424, 1384, 1372, 1341, 1328, 1316, 1303, 1269, 1255, 1234, 1196, 1177, 1138, 1099, 1056, 994, 976, 885, 852, 819, 784, 764, 740, 710 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.56 [s, 9 H, $C(CH_3)_3$], 2.70 (t, *J* = 6.2 Hz, 2 H, CH_2), 3.78 (t, *J* = 6.2 Hz, 2 H, CH_2), 3.71 (s, 3 H, CH_3), 5.20 (s, 2 H, CH_2), 8.10 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 34.0, 44.0, 53.2, 68.7, 84.1, 130.2, 132.7, 148.2, 148.7, 155.3, 172.0.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{19}ClN_4O_4$: 342.1095; found: 342.1098.

3-(9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydropurin-7-yl)propanenitrile (5b)

Following the general procedure, starting from **2a** (1.285 g, 5.0 mmol), acrylonitrile (0.530 g, 10.0 mmol), DBU (0.912 g, 6.0 mmol), and anhyd MeCN (20 mL), the title compound was obtained after column chromatography (silica gel, hexane–EtOAc, 1:1) as a white solid; yield: 1.347 g (97%); mp 93–96 °C.

IR (ATR): 2979, 2935, 2880, 1709, 1598, 1569, 1476, 1454, 1426, 1395, 1371, 1342, 1300, 1258, 1154, 1095, 1050, 886, 835, 762, 728 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.56 [s, 9 H, $C(CH_3)_3$], 2.73 (t, *J* = 6.6 Hz, 2 H, CH_2), 3.82 (t, *J* = 6.6 Hz, 2 H, CH_2), 5.31 (s, 2 H, CH_2), 8.17 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 28.3, 44.6, 69.7, 84.5, 117.7, 129.5, 133.4, 148.0, 149.5, 155.3.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}ClN_5O_2$: 309.0993; found: 309.0994.

9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydro-7-(3-oxobutyl)purine (5c)

Following the general procedure, starting from **2a** (1.285 g, 5.0 mmol), but-3-en-2-one (0.70 g, 10.0 mmol), DBU (0.912 g, 6.0 mmol), and anhyd MeCN (20 mL), the title compound was obtained after column chromatography (silica gel, hexane–EtOAc, 1:1) as a white solid; yield: 1.418 g (95%); mp 115–118 °C.

IR (ATR): 2984, 2939, 2860, 1706, 1667, 1598, 1573, 1499, 1465, 1425, 1370, 1352, 1295, 1251, 1167, 1154, 1096, 1068, 1050, 986, 927, 888, 851, 760, 728 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.56 [s, 9 H, $C(CH_3)_3$], 2.22 (s, 3 H, CH_3), 2.85 (t, *J* = 6.0 Hz, 2 H, CH_2), 3.71 (t, *J* = 6.0 Hz, 2 H, CH_2), 5.20 (s, 2 H, CH_2), 8.09 (s, 1 H, H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 30.5, 42.6, 43.2, 69.9, 84.0, 130.4, 132.1, 148.1, 148.4, 155.3, 206.8.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{19}ClN_4O_3$: 326.1146; found: 326.1146.

Deprotection and Oxidation of N^7-Substituted Dihydropurines 3 and 5; General Procedure

N^7-Substituted dihydropurine **3** or **5** (1 mmol, 1.0 equiv) was added to a solution of trifluoroacetic acid (1 mL/mmol) in anhyd CH_2Cl_2 (1 mL/mmol). The mixture was stirred for 90 min at r.t., and concentrated in vacuo. Subsequently, CH_2Cl_2 (20 mL/mmol) was added and the organic layer was washed with sat. aq $KHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), and concentrated in vacuo. The crude product was mixed with MnO_2 (5 mmol, 5.0 equiv) and CH_2Cl_2 (5 mL/mmol), stirred for 1 h at r.t., concentrated in vacuo, and the product was purified by column chromatography.

Simplified Preparation of N^7-Substituted Purines from 9-*tert*-Butoxycarbonyl-6-chloro-7,8-dihydropurine (2a) without Purification of Intermediates; General Procedure

N^7-Substituted dihydropurines **3** and **5** were prepared following the general procedures for the alkylation and the Michael addition of **2a**. Crude N^7-alkylated-7,8-dihydropurine **3** or **5**, obtained by evaporation of the solvents, was dissolved in anhyd CH_2Cl_2 (1 mL/mmol) followed by the addition of trifluoroacetic acid (1 mL/mmol). The mixture was then stirred for 90 min at r.t., and concentrated in vacuo. Subsequently, CH_2Cl_2 (20 mL/mmol) was added and the organic layer was washed with sat. aq $KHCO_3$ (20 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the com-

bined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product obtained was mixed with MnO_2 (5.0 equiv) and CH_2Cl_2 (5 mL/mmol), stirred for 1 h at r.t., and concentrated in vacuo. Column chromatography of the residue gave the desired N^7-substituted purine **6**.

6-Chloro-7-methyl-7*H*-purine (6a)
Following the general procedure, starting from **3a** (0.271 g, 1.0 mmol) and MnO_2 (0.435 g, 5.0 mmol), the title compound was obtained after column chromatography (silica gel, EtOAc–MeOH, 20:1) as a white solid; yield: 0.157 g (92%); mp 200–202 °C (Lit.[19] mp 198–199 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.10 (s, 3 H, CH_3), 8.74 (s, 1 H, Pu-H), 8.80 (s, 1 H, Pu-H); in accordance with the literature.[20]

7-Benzyl-6-chloro-7*H*-purine (6b)
Following the general procedure, starting from **3c** (0.347 g, 1.0 mmol) and MnO_2 (0.435 g, 5.0 mmol), the title compound was obtained after column chromatography (silica gel, EtOAc–MeOH, 20:1) as a white solid; yield: 0.229 g (94%); mp 150–152 °C (Lit.[21] mp 153–154 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.75 (s, 2 H, CH_2), 7.1–7.2 (m, 2 H, C_6H_5) 7.3–7.4 (m, 3 H, C_6H_5), 8.81 (s, 1 H, Pu-H), 9.00 (s, 1 H, Pu-H); in accordance with the literature.[21]

7-Allyl-6-chloro-7*H*-purine (6c)
Following the general procedure, starting from **3d** (0.297 g, 1.0 mmol) and MnO_2 (0.435 g, 5.0 mmol), the title compound was obtained after column chromatography (silica gel, EtOAc–MeOH, 20:1) as a white solid; yield: 0.181 g (93%); mp 93 °C (Lit.[7] mp 93–94 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.13 (m, 2 H, CH_2), 5.1–5.3 (m, 2 H, CH_2), 6.08 (m, 1 H, =CH), 8.31 (s, 1 H, Pu-H), 8.75 (s, 1 H, Pu-H); in accordance with the literature.[22]

6-Chloro-7-propargyl-7*H*-purine (6d)
Following the general procedure, starting from **3e** (0.295 g, 1.0 mmol) and MnO_2 (0.435 g, 5.0 mmol), the title compound was obtained after column chromatography (silica gel, EtOAc–MeOH, 20:1) as a yellow solid; yield: 0.175 g (91%); mp 108–111 °C (Lit.[11] white foam, no mp given).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68 (t, *J* = 1.2 Hz, 1 H, ≡CH), 5.29 (d, *J* = 1.2 Hz, 2 H, CH_2), 8.48 (s, 1 H, Pu-H), 8.90 (s, 1 H, Pu-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.5, 75.3, 77.6, 122.4, 143.4, 148.7, 152.9, 162.3; in accordance with the literature.[11]

Methyl 3-(6-Chloro-7*H*-purin-7-yl)propionate (6e)
Following the general procedure, starting from **5a** (0.343 g, 1.0 mmol) and MnO_2 (0.435 g, 5.0 mmol), the title compound was obtained after column chromatography (silica gel, EtOAc–MeOH, 20:1) as a white solid; yield: 0.232 g (97%); mp 76–78 °C.

IR (ATR): 2997, 2960, 2937, 2857, 1725, 1688, 1595, 1536, 1485, 1451, 1410, 1389, 1372, 1329, 1289, 1242, 1207, 1181, 1080, 1065, 1003, 974, 936, 887, 850, 835, 796, 736, 679 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.97 (t, *J* = 6.0 Hz, 2 H, CH_2), 3.66 (s, 3 H, CH_3), 4.77 (t, *J* = 6.0 Hz, 2 H, CH_2), 8.38 (s, 1 H, Pu-H), 8.85 (s, 1 H, Pu-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.6, 42.8, 52.6, 122.3, 142.8, 150.4, 152.8, 162.4, 170.9.

HRMS (EI): *m*/*z* calcd for $C_9H_9ClN_4O_2$: 240.0414; found: 240.0417.

(6-Chloro-7*H*-purin-7-yl)propanenitrile (6f)
Following the general procedure, starting from **5b** (0.310 g, 1.0 mmol) and MnO_2 (0.435 g, 5.0 mmol), the title compound was obtained after column chromatography (silica gel, EtOAc–MeOH, 20:1) as a white solid; yield: 0.189 g (91%); mp 160–163 °C.

IR (ATR): 3106, 2962, 2927, 1672, 1595, 1537, 1485, 1453, 1422, 1382, 1368, 1326, 1284, 1249, 1213, 1181, 1165, 1080, 1002, 975, 924, 903, 847, 822, 796, 731 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.20 (t, *J* = 6.6 Hz, 2 H, CH_2), 4.77 (t, *J* = 6.6 Hz, 2 H, CH_2), 8.82 (s, 1 H, Pu-H), 8.86 (s, 1 H, Pu-H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.5, 42.7, 118.7, 122.6, 143.0, 151.6, 152.5, 162.2.

HRMS (EI): *m*/*z* calcd for $C_8H_6ClN_5$: 207.0312; found: 207.0305.

6-Chloro-7-(3-oxobutyl)-7*H*-purine (6g)
Following the general procedure, starting from **5c** (0.327 g, 1.0 mmol) and MnO_2 (0.435 g, 5.0 mmol), the title compound was obtained after column chromatography (silica gel, EtOAc–MeOH, 20:1) as a yellow solid; yield: 0.195 g (87%); mp 122–124 °C.

IR (ATR): 3242, 3143, 3075, 2952, 2765, 1680, 1662, 1643, 1616, 1543, 1501, 1456, 1437, 1423, 1364, 1345, 1316, 1278, 1215, 1192, 1163, 1134, 1061, 1014, 983, 833, 799, 780, 764, 720, 689 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 3.10 (t, *J* = 7.1 Hz, 2 H, CH_2), 4.74 (t, *J* = 7.1 Hz, 2 H, CH_2), 8.41 (s, 1 H, Pu-H), 8.86 (s, 1 H, Pu-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.4, 41.5, 44.3, 122.3, 142.7, 151.1, 152.5, 162.2, 205.1.

HRMS (EI): *m*/*z* calcd for $C_9H_9ClN_4O$: 224.0465; found: 224.0460.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are ^{1}H and ^{13}C NMR spectra of **1b**, **2a**, **2b**, **3a–j**, **4a–e**, **5a–c**, **6a–g**.

Acknowledgment

This project was supported by the Research Centre 'The Structure and Synthetic Applications of Transition Metal Complexes–LC06070' of the Ministry of Education, Youth, and Sports of the Czech Republic, by the Grant Agency of the Czech Republic (grant no. 203/09/1552), and by Specific University Research (MSMT No. 21/2011).

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