Monatsh Chem (2013) 144:501–507
DOI 10.1007/s00706-012-0899-x

ORIGINAL PAPER

Regioselective and efficient synthesis of N^7-substituted adenines, guanines, and 6-mercaptopurines

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Received: 15 October 2012 / Accepted: 4 December 2012 / Published online: 1 February 2013

Abstract A simple and efficient protocol for the preparation of N^7-substituted adenines, guanines, and 6-mercaptopurines is described. The key step is the regioselective preparation of 7-substituted 6-chloropurines which are building blocks for the divergent synthesis of adenines, guanines, and 6-mercaptopurines by known procedures.

Keywords Heterocycles · Nucleophilic substitution · Alkylation · Staudinger reaction

Introduction

Purine is a well-known heterocyclic scaffold which frequently occurs in nature [1] as well as a part of biologically active compounds. The biological activity of natural purine compounds has led to systematic studies of the properties and reactivity of novel purine derivatives [2–9]. Therefore, it is not surprising that N^9-substituted adenines, hypoxathines, and guanines exhibit interesting biological activities. In view of these findings, some N^7-substituted adenines have been designed, prepared, and tested for their biological properties [10–13]. Indeed, some N^7-substituted adenines showed antiviral [14, 15] and anticancer [16] activities. In addition, A_{2A} and A_{2B} receptor ligands [17], VEGF-R and EGF-R inhibitors [18], ATP-competitive kinase inhibitors [19], and inhibitory activity against pathogenic protozoa [20] have been described in the literature. Some N^7-substituted 6-mercaptopurines also show cytotoxic activity [21, 22] and 6-chloro-7-methyl-7*H*-purine is a radiolabeled probe for assessing glutathione-conjugate efflux systems in the brain [23]. Besides that, various N^7-substituted adenines and guanines have been prepared as standards of DNA adducts of the styrene metabolites [24–27].

The classical approaches to N^7-substituted purines rely on the laborious cyclization of diaminopyrimidine derivatives [28] or on the direct alkylation of simple purine bases which, however, usually affords a mixture of regioisomers. Thus, adenine is preferentially N^3-alkylated [29] and alkylation of hypoxanthine produces a mixture of mono- and disubstituted products [29–33]. Only in several limited cases can significantly regioselective formation of N^7-substituted adenines, guanines, and hypoxanthines be achieved. For instance, the alkylation of N^3-benzyladenine followed by debenzylation affords N^7-substituted adenines [34, 35] and the alkylation of N^6-[(dimethylamino)methylene]adenine proceeds exclusively at the N^7-position [36]. Temporary N^9-protection of adenine and guanine by a trityl protecting group followed by the reaction with strong alkylating reagents also enables a regioselective way to N^7-substituted adenines and guanines [15].

However, the scope of the reported protocols is limited. As a part of our ongoing research activities we have developed [37, 38] an easy and high-yielding methodology for the synthesis of N^7-substituted 6-chloropurines. The presence of a halogen in a series of readily available 7-alkyl-6-chloro-7*H*-purines can be, in principle, used for further derivatization to obtain 7-substituted adenine, hypoxanthine, and guanine derivatives. Therefore, we decided to test the combination of our protocol for the synthesis of 7-substituted 6-halopurines with subsequent halogen displacement by known methods for the preparation of new

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N^7-substituted adenine, hypoxanthine, or guanine derivatives with potential biological activities.

Results and discussion

The following described protocol [37, 38] is based on the conversion of 6-chloropurine (**1a**) and 6-chloropurine-2-amine (**1b**) to the corresponding 9-Boc derivatives, reduction to the 7,8-dihydropurines, their N^7-alkylation followed by deprotection and oxidation. 7-Alkylpurines **2a**–**2f**, **3b**, and **3d** were obtained in 54–78 % isolated yields. At first we focused on the preparation of hypoxanthine analogues. Heating of **2a**–**2e** with formic acid [39] led to the 7-substituted purines **4a**–**4e** in almost quantitative yields (Table 1, entries 1–5; Scheme 1). The reaction conditions are compatible with methyl, allyl, and propargyl groups (Table 1, entries 1–3) but also ester and keto groups (Table 1, entries 4, 5). The reaction of 7-substituted 6-chloropurine-2-amines **3b** and **3d** was also smooth giving the guanine derivatives **5b** and **5d** in almost quantitative yield (Table 1, entries 5, 6). Table 1 also shows the overall yields of the derivatives **4** and **5**, starting from **1a** or **1b**, respectively, which are 51–73 %.

The above results encouraged us to test the reaction of 7-substituted chloropurines with NaSH. Thus, a series of 7-substituted 6-chloro-7*H*-purines **2a**, **2d**, **2e**, **3b**, and **3d** were treated with a solution of NaSH in dry DMF at ambient temperature. TLC analysis of the crude reaction mixture revealed complete conversion of the starting materials to the mercaptopurines **6** and **7** within 2 h. The isolated yields were almost quantitative (Table 2).

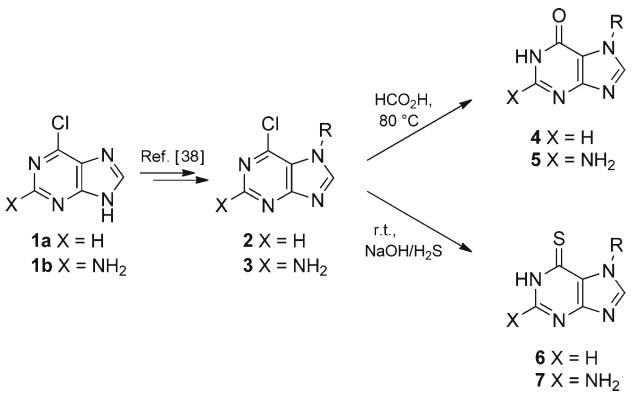
The most straightforward route to the substituted adenines from halopurines is halogen displacement of halopurines with ammonia [40], but this involves harsh reaction conditions. Therefore, we used a two-step protocol

Table 1 Regioselective synthesis of N^7-substituted hypoxanthines **4** and N^7-substituted guanines **5** starting from N^7-substituted halopurines **2** or **3**

Entry	Starting compound, R (yield/% from **1a** or **1b**) [38]	Product, yield/%[a] (overall yield/%)[b]
1	**2a**, Me (77)	**4a**, 95 (73)
2	**2b**, CH_2=$CHCH_2$ (78)	**4b**, 87 (68)
3	**2c**, $HCCCH_2C$ (76)	**4c**, 93 (71)
4	**2d**, CH_3CHCO_2Me (62)	**4d**, 90 (56)
5	**2e**, $C_6H_5COCH_2$ (54)	**4e**, 94 (51)
6	**3b**, CH_2=$CHCH_2$ (58)	**5b**, 96 (56)
7	**3d**, CH_3CHCO_2Me (72)	**5d**, 97 (70)

[a] Isolated yield

[b] Overall isolated yield starting from **1a** or **1b**



Scheme 1

Table 2 Synthesis of N^7-substituted 6-mercaptopurines **6** and **7** starting from N^7-substituted halopurines **2** or **3**

Entry	Starting compound, R	Product, yield/%[a] (overall yield/%)[b]
1	**2a**, CH_3	**6a**, 96 (74)
2	**2d**, CH_3CHCO_2Me	**6d**, 97 (60)
3	**2e**, $C_6H_5COCH_2$	**6e**, 97 (52)
4	**3b**, CH_2=$CHCH_2$	**7b**, 89 (52)
5	**3d**, CH_3CHCO_2Me	**7d**, 87 (63)

[a] Isolated yield

[b] Overall isolated yield starting from **1a** or **1b**

relying on the chemistry of azides [41–43]. The first step, reaction of the chloropurines **2b**, **2d**–**2f**, and **3b** with sodium azide, proceeded smoothly in DMSO at 60 °C (Scheme 2) and the corresponding azides were isolated in high yields (Table 3). An exception was the substrates bearing phenacyl and allyl groups (**8e** and **9b**, respectively), which were formed in only moderate yields of 54 and 74 % (Table 3, entries 3, 5). The structure of the obtained azides was confirmed using ^{1}H and ^{13}C NMR, which showed the previously reported azido-purine fused tetrazole tautomerism [41–43]. The azide reduction appeared to be more complicated. The palladium-catalyzed hydrogenation, offering a simple and efficient method [44, 45], failed in this case, because the allylic double bond in **3b** was hydrogenated together with the azide. Therefore, we turned our attention to the Staudinger reaction which is compatible with a wide variety of functional groups. Thus, the reaction of **8f** with triphenylphosphine in THF at 60 °C furnished the expected azaphosphorane **13** in 95 % yield (Fig. 1). Its structure was determined by ^{1}H and ^{13}C NMR spectroscopy. The hydrolysis of **13** in a mixture of acetic acid/THF/water (2:6:1) proceeded smoothly, and the desired aminopurine **10f** was isolated in 97 % yield. The structure of **10f** was proved by ^{1}H, ^{13}C NMR along with HMBC and HMQC correlations. The above two-step

Scheme 2

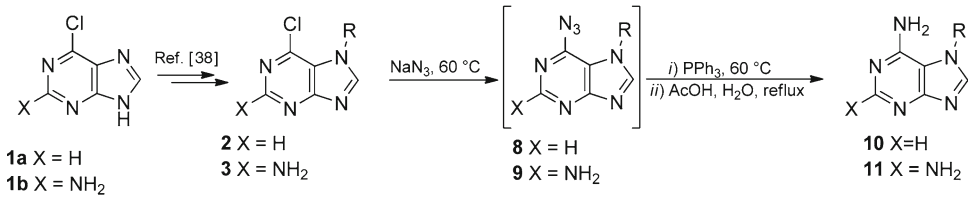


Table 3 Synthesis of N^7-substituted adenines **10** and **11** starting from N^7-substituted halopurines **2** and **3**

Entry	Starting compound, R	Product, yield/%[a]	Product, yield/%[b]	Overall yield/%[c]
1	**2b**, CH_2=$CHCH_2$	**8b**, 89	**10b**, 85	59
2	**2d**, CH_3CHCO_2Me	**8d**, 95	**10d**, 75[d]	44
3	**2e**, $C_6H_5COCH_2$	**8e**, 54	**10e**, 58	17
4	**2f**, $C_6H_5CH_2$	**8f**, 96	**10f**, 90	74
5	**3b**, CH_2=$CHCH_2$	**9b**, 74	**11b**, 85	36

[a] Overall isolated yield from **1a** or **1b**

[b] Overall isolated yield from **2** or **3**

[c] Overall isolated yield from **1a** or **1b**

[d] R = CH_3CHCO_2H

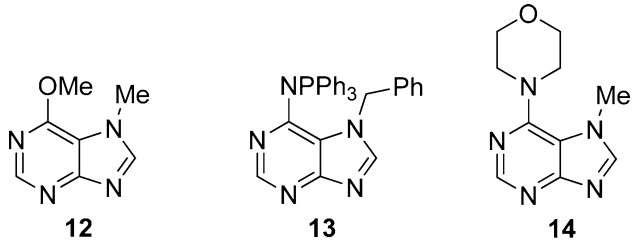


Fig. 1 Structures of 7-substituted purines **12–14**

reaction can also be done in a one-pot manner. In this way the reflux of **8f** and triphenylphosphine in an acetic acid/THF/water mixture for 24 h gave **10f** in 90 % yield (Table 3, entry 4). This one-pot protocol was also successfully applied to the transformation of **8b** and **9b** to **10b** and **11b**, respectively, in 85 % yields (Table 3, entries 1, 5). In the case of the phenacylpurine **8e** the yield of **10e** was 58 % because the product was isolated from a complex reaction mixture by tedious chromatography. Interestingly, the formation of acid **10d** along with azido to amino group transformation was observed during the reaction. In addition, N^6-alkyladenines are available via reaction of 7-substituted 6-chloropurines with *N*-alkylamines as demonstrated by the reaction of **2a** with morpholine in acetonitrile at 70 °C, where the corresponding morpholinopurine **14** (Fig. 1) was isolated in 94 % yield. Similarly, 6-chloro-7-methylpurine reacted smoothly with sodium methoxide in dry methanol at room temperature affording 6-methoxy-7-methyl-7*H*-purine (**12**) in 91 % isolated yield (Fig. 1).

In summary, we showed that the combination of our protocol for the regioselective synthesis of 7-alkyl-6-chloropurines with known procedures for the nucleophilic displacement of the chlorine in 6-chloropurines can be used as a versatile tool for the synthesis of N^7-substituted adenines, guanines, hypoxanthines, and 6-mercaptopurines from 6-chloropurine (**1a**) or 6-chloropurine-2-amine (**1b**). Hypoxanthines **4a–4e**, **5b**, and **5d** were prepared by heating chloropurines **2** or **3** with formic acid. The overall yields of **4a–4e**, **5b**, and **5d** starting from **1a** and **1b** ranged from 51 to 73 %. 6-Mercaptopurines **6a–e**, **7b**, and **7d** were prepared by the reaction of **2** or **3** with sodium hydrosulfide in 52–74 % overall yields. Finally, the preparation of 7-substituted adenines was achieved by a two-step protocol based on the Staudinger reaction. In the first step 6-chloropurines **2** and **3** were converted to the corresponding azides **8** and **9** by the reaction with sodium azide. The second step, one-pot Staudinger reaction, was achieved by refluxing of azides **8b**, **8d–8f**, or **9b** with triphenylphosphine in acetic acid/THF/water. In this way N^7-substituted adenines **10b**, **10d–10f**, and **11b** were prepared in 17–60 % overall yields starting from **1a** and **1b**. Further application of 7,8-dihydropurines in the synthesis of novel purine derivatives and their biological evaluation is ongoing in our laboratory.

Experimental

All reactions were performed under an argon atmosphere. ^{1}H (300 or 500 MHz) and ^{13}C (75 or 125 MHz) NMR spectra were measured on Varian Gemini 300 or Bruker Avance III 500 instrument. Mass spectra (HRMS-ESI) were recorded on a 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. The starting compounds **2a–2f**, **3b**, and **3d** were prepared according to the reported protocol [38]. In case of **3b** and **3d** NaH was used instead of LiHMDS.

Methyl 2-(6-chloropurine-7-yl)propanoate (**2d**, $C_9H_9ClN_4O_2$)

White solid; 0.912 g (62 % overall yield from **1a**); m.p.: 67–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.95$ (d, $J = 7.8$ Hz, 3H, CH_3), 8.47 (s, 1H, CH^{Pu}), 8.78 (s, 1H,

CH^{Pu}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.0$, 53.3, 54.9, 122.2, 142.7, 147.2, 152.3, 161.6, 169.9 ppm; HRMS (ESI): *m/z* calcd for $C_9H_9ClN_4NaO_2$ 263.03062, found 263.03074.

6-Chloro-7-phenacylpurine (**2e**, $C_{13}H_9ClN_4O$)
Yellow solid; 0.661 g (54 % overall yield from **1a**); m.p.: 187 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6): $\delta = 6.25$ (s, 2H, CH_2), 7.65 (m, 2H, CH^{Ph}), 7.75 (m, 1H, CH^{Ph}), 8.10 (m, 2H, CH^{Ph}), 8.74 (s, 1H, CH^{Pu}), 8.84 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 53.3$, 122.8, 128.2, 129.2, 133.6, 134.6, 151.6, 151.8, 161.5, 193.1 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_9ClN_4NaO$ 295.03571, found 295.03586.

7-Allyl-6-chloropurine-2-amine (**3b**, $C_8H_8ClN_5$)
Yellow solid; 0.170 g (58 % overall yield from **1b**); m.p.: 180 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6): $\delta = 4.90$ (m, 3H, CH and CH_2), 5.17 (d, $J = 10.5$ Hz, 1H, CH), 6.05 (m, 1H, CH), 6.63 (br s, 2H, NH_2), 8.36 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 48.2$, 115.1, 117.1, 134.4, 142.5, 149.7, 160.2, 164.3 ppm; HRMS (ESI): *m/z* calcd for $C_8H_8ClN_5Na$ 232.03604, found 232.03688.

Methyl 2-(2-amino-6-chloropurine-7-yl)propanoate (**3d**, $C_9H_{10}ClN_5O_2$)
Yellow solid; 0.172 g (72 % overall yield from **1b**); ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.81$ (d, $J = 7.2$ Hz, 3H, CH_3), 3.69 (s, 3H, CH_3), 5.61 (q, $J = 7.2$ Hz, 1H, CH), 6.68 (s, 2H, NH_2), 8.50 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 17.1$, 53.0, 55.7, 107.4, 140.3, 151.3, 153.1, 153.8, 169.6 ppm.

General procedure for conversion of N^7-substituted 6-chloropurines to N^7-substituted hypoxanthines

A solution of starting 6-chloropurine **2** or **3** (1 mmol) in 10 cm^3 of formic acid was heated for 2 h at 75 °C. The mixture was evaporated in vacuo, 10 cm^3 of ethanol was added, and the resultant mixture was refluxed for 30 min. Evaporation under reduced pressure and column chromatography (silica gel, dichloromethane/methanol, 10:1) gave the final product.

7-Methylhypoxanthine (**4a**)
White solid; 0.428 g (95 %); m.p.: >270 °C (Ref. [40] 355–357 °C); ^1H NMR in accordance with the literature data [46].

7-Allylhypoxanthine (**4b**, $C_8H_8N_4O$)
White solid; 0.153 g (87 %); m.p.: 236–237 °C; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 4.94$–5.07 (m, 3H, CH_2, CH_2), 5.18 (m, 1H, CH_2), 6.09 (m, 1H, CH), 7.96 (s, 1H, CH^{Pu}), 8.21 (s, 1H, CH^{Pu}), 12.30 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 48.2$, 114.8, 117.4, 134.2, 143.7, 144.6, 154.3, 157.1 ppm; HRMS (ESI): *m/z* calcd for $C_8H_8N_4NaO$ 199.05903, found 199.05903.

7-Propargylhypoxanthine (**4c**, $C_8H_6N_4O$)
White solid; 0.127 g (93 %); m.p.: 236 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6): $\delta = 3.54$ (t, 1H, $J = 2.3$ Hz, CH), 5.24 (d, 2H, $J = 2.3$ Hz, CH_2), 7.99 (s, 1H, CH^{Pu}), 8.30 (s, 1H, CH^{Pu}), 12.39 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 35.8$, 76.7, 78.2, 114.6, 143.4, 144.9, 154.2, 157.0 ppm; HRMS (ESI): *m/z* calcd for $C_8H_6N_4NaO$ 197.04338, found 197.04337.

Methyl 2-(1,6-dihydro-6-oxopurine-7-yl)propionate (**4d**, $C_9H_{10}N_4O_3$)
White solid; 0.418 g (90 %); m.p.: 189–191 °C; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.78$ (d, 3H, $J = 7.3$ Hz, CH_3), 3.66 (s, 3H, CH_3), 5.65 (q, 1H, $J = 7.3$ Hz, CH), 8.00 (s, 1H, CH^{Pu}), 8.34 (s, 1H, CH^{Pu}), 12.35 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 17.7$, 52.7, 54.7, 114.9, 143.1, 144. 8, 154.2, 157.3, 170.4 ppm; HRMS (ESI): *m/z* calcd for $C_9H_{10}N_4NaO_3$ 245.06451, found 245.06456.

7-Phenacylhypoxanthine (**4e**, $C_{13}H_{10}N_4O_2$)
White solid; 0.119 g (94 %); m.p.: 261 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6): $\delta = 6.03$ (s, 2H, CH_2), 7.62 (m, 2H, ArH), 7.76 (m, 1H, ArH), 7.99 (s, 1H, CH^{Pu}), 8.07 (m, 2H, CH^{Ar}), 8.17 (s, 1H, CH^{Pu}), 12.31 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 52.9$, 115.6, 128.1, 129.1, 134.0, 134.2, 144.6, 144.7, 154.4, 156.9, 192.7 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_{10}N_4NaO_2$ 277.06960, found 277.06965.

7-Allylguanine (**5b**, $C_8H_9N_5O$)
Beige solid; 0.185 g (96 %); m.p.: >270 °C; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 4.80$ (d, $J = 5.4$ Hz, 2H, CH_2), 5.00 (d, $J = 17.1$ Hz, 1H, CH), 5.14 (d, $J = 10.8$ Hz, 1H, CH), 6.26 (s, 2H, NH_2), 7.86 (s, 1H, CH^{Pu}), 10.89 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 47.9$, 107.9, 117.1, 134.4, 142.7, 153.1, 154.4, 159.7 ppm; HRMS (ESI): *m/z* calcd for $C_8H_9N_5NaO$ 214.06993, found 214.07056.

Methyl 2-(2-amino-1,6-dihydro-6-oxopurine-7-yl)propanoate (**5d**, $C_9H_{11}N_5O_3$)
White solid; 0.027 g (97 %); m.p.: 261 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.71$ (d, $J = 7.3$ Hz, 3H, CH_3), 3.63 (s, 3H, CH_3), 5.49 (q, $J = 7.3$ Hz, 1H, CH), 6.51 (br s, 2H, NH_2), 8.01 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 17.6$, 52.5, 54.3, 107.9, 142.1, 153.3, 154.5, 159.9, 170.6 ppm; HRMS (ESI): *m/z* calcd for $C_9H_{11}N_5NaO_3$ 260.07541, found 260.07633.

General procedure for conversion of N^7-substituted 6-chloropurines to N^7-substituted 6-mercaptopurines

NaSH (1.25 cm^3, 4 M solution in water) was added to a solution of 6-chloropurine **2** or **3** (1 mmol) in 6 cm^3 DMF. The resultant mixture was stirred for 80 min at ambient temperature and then 1 cm^3 HCl (1 M) was added. Evaporation under reduced pressure and flash chromatography (silica gel, dichloromethane/methanol, 10:1) gave the final product.

7-Methyl-6-mercaptopurine (**6a**)
White solid; 0.080 g (96 %); m.p.: >270 °C (Ref. [46] 306–308 °C); NMR spectra in accordance with the literature data [47].

Methyl 2-(6-mercaptopurine-7-yl)propanoate (**6d**, $C_9H_{10}N_4O_2S$)
Yellow solid; 0.114 g (96 %); m.p.: 212–215 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.85$ (d, 3H, $J = 7.3$ Hz, CH_3), 3.68 (s, 3H, CH_3), 6.66 (m, 1H, CH), 8.21 (d, 1H, $J = 1.2$ Hz, CH^{Pu}), 8.71 (s, 1H, CH^{Pu}), 13.79 (br s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 17.4$, 52.8, 54.6, 125.2, 145.2, 146.7, 153.0, 169.9, 170.7 ppm; HRMS (ESI): *m/z* calcd for $C_9H_{10}N_4NaO_2S$ 261.04167, found 261.04177.

6-Mercapto-7-phenacylpurine (**6e**, $C_{13}H_{10}N_4OS$)
White solid; 0.118 g (97 %); m.p.: 264 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 6.42$ (s, 1H, CH_2), 7.62 (m, 2H, CH^{Ar}), 7.74 (m, 1H, CH^{Ar}), 8.07 (m, 2H, ArH), 8.21 (s, 1H, CH^{Pu}), 8.44 (s, 1H, CH^{Pu}), 13.77 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 53.5$, 125.6, 128.1, 129.1, 134.1, 134.1, 145.1, 149.0, 152.8, 169.9, 192.7 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_{10}N_4NaOS$ 293.04675, found 293.04666.

7-Allyl-6-mercaptopurine-2-amine (**7b**, $C_8H_9N_5S$)
Yellow solid; 0.185 (89 %); m.p.: >270 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 4.94$ (dd, $J = 1.2$, 17.1 Hz, 1H, CH), 5.14 (dd, $J = 1.2$, 10.2 Hz, 1H, CH), 5.22 (d, $J = 5.4$ Hz, 2H, CH_2), 6.05 (m, 1H, CH), 6.49 (br s, 2H, NH_2), 8.14 (s, 1H, CH^{Pu}), 11.94 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 48.1$, 117.1, 119.3, 135.1, 148.0, 153.3, 156.9, 169.0 ppm; HRMS (ESI): *m/z* calcd for $C_8H_{10}N_5S$ 208.06514, found 208.06501.

Methyl 2-(2-amino-6-mercaptopurine-7-yl)propanoate (**7d**, $C_9H_{11}N_5O_2S$)
White solid; 0.220 g (87 %); m.p.: 244–246 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.76$ (d, $J = 7.5$ Hz, 3H, CH_3), 3.64 (s, 3H, CH_3), 6.53 (br s, 2H, NH_2), 8.36 (s, 1H, CH^{Pu}), 11.99 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 18.8$, 52.9, 54.4, 119.5, 146.8, 153.3, 157.1, 168.9, 171.1 ppm; HRMS (ESI): *m/z* calcd for $C_9H_{11}N_5NaO_2S$ 276.05257, found 276.05365.

*General procedure for reaction of 6-chloropurines **2** and **3** with sodium azide*

Dimethylsulfoxide (4 cm^3) was added to a mixture of halopurine **2** or **3** (1 mmol) and 0.195 g NaN_3 (3 mmol). The resultant mixture was heated for 3 h at 60 °C, diluted with 80 cm^3 ethyl acetate, and the organic layer was washed with brine (3 × 30 cm^3). Then the collected water layers were extracted with ethyl acetate and the collected organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (silica gel, ethyl acetate/methanol, 20:1) gave the final product.

7-Allyl-6-azidopurine (**8b**, $C_8H_7N_7$)
White solid; 0.154 g (89 %); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.19$–5.30 (m, 4H, 2 × CH_2), 6.05 (m, 1H, CH), 8.25 (1H, CH^{Pu}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 50.0$, 111.3, 120.4, 130.5, 133.3, 141.9, 144.1, 151.0 ppm.

Methyl 2-(6-azidopurine-7-yl)propanoate (**8d**, $C_9H_9N_7O_2$)
White solid; 0.237 g (95 %); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.00$ (d, $J = 7.4$ Hz, 3H, CH_3), 3.70 (s, 3H, CH_3), 5.94 (q, $J = 7.4$ Hz, 1H, CH), 8.76 (s, 1H, CH^{Pu}), 10.07 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 17.6$, 53.5, 56.3, 111.3, 135.9, 142.7, 145.6, 151.6, 170.2 ppm.

6-Azido-7-phenacylpurine (**8e**, $C_{13}H_9N_7O$)
Yellow solid; 0.140 g (54 %); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 6.39$ (s, 2H, CH_2), 7.70 (m, 2H, CH^{Ar}), 7.80 (m, 1H, CH^{Ar}), 8.17 (d, $J = 7.4$ Hz, 2H, CH^{Ar}), 8.65 (s, 1H, CH^{Pu}), 10.07 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 54.3$, 112.6, 127.9, 128.7, 129.7, 131.7, 134.3, 135.1, 135.7, 142.5, 146.7, 151.3 ppm.

6-Azido-7-benzylpurine (**8f**, $C_{12}H_9N_7$)
White solid; 0.420 g (96 %); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.80$ (s, 2H, CH_2), 7.30 (m, 3H, CH^{Ar}), 7.50 (m, 2H, CH^{Ar}), 8.87 (s, 1H, CH^{Pu}), 9.99 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 50.7$, 111.4, 128.1, 128.4, 129.0, 135.3, 136.1, 142.4, 145.5, 151.2 ppm.

7-Allyl-6-azidopurine-2-amine (**9b**, $C_8H_8N_8$)
White solid; 0.160 g (74 %); ^{1}H NMR (600 MHz, DMSO-d_6): $\delta = 5.07$ (s, $J = 5.2$ Hz, 2H, CH_2), 5.16 (d, $J = 16.0$ Hz, 1H, CH), 5.23 (d, $J = 10.2$ Hz, 1H, CH), 6.15 (m, 1H, CH), 8.04 (br s, 2H, NH_2), 8.31 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): $\delta = 48.9$, 104.0, 118.3, 133.0, 142.7, 142.9, 143.8, 153.5 ppm.

General procedure for preparation of 7-substituted adenines and guanines via Staudinger reaction

Triphenylphosphine (2 mmol) was added to a solution of azides **8b**, **8d–8f**, or **9b** (1 mmol) in AcOH/THF/H_2O

(2:6:1 cm^3). The resultant mixture was refluxed for 24 h and concentrated in vacuo. Separation by column chromatography (silica gel, ethyl acetate/methanol, 6:4) afforded the final product.

7-Allyladenine (**10b**, $C_8H_9N_5$)
White solid; 0.160 g (85 %); m.p.: 194–196 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.86$ (d, $J = 17.3$ Hz, 1H, CH), 5.07 (d, $J = 4.9$ Hz, 2H, CH_2), 5.17 (dd, $J = 0.65$, 10.5 Hz, 1H, CH), 6.05 (m, 1H, CH), 6.84 (br s, 2H, NH_2), 8.19 (s, 1H, CH^{Pu}), 8.26 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 48.5$, 111.3, 117.0, 135.4, 146.3, 151.8, 152.8, 160.4 ppm; HRMS (ESI): *m/z* calcd for $C_8H_9N_5Na$ 198.07502, found 198.07561.

2-(6-Aminopurine-7-yl)propanoic acid (**10d**, $C_8H_9N_5O_2$)
White solid; 0.112 g (75 %); m.p.: 211–216 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.55$ (d, $J = 7.2$ Hz, 3H, CH_3), 4.86 (q, $J = 7.5$ Hz, 1H, CH), 8.13 (s, 1H, CH^{Pu}), 8.22 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 19.2$, 59.9, 111.9, 144.5, 151.9, 152.8, 159.9, 172.7 ppm; HRMS (ESI): *m/z* calcd for $C_8H_9N_5NaO_2$ 230.06485, found 230.06561.

7-Phenacyladenine (**10e**, $C_{13}H_{11}N_5O$)
Yellow solid; 0.074 g (58 %); m.p.: 230 °C (decomp.); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 6.19$ (s, 2H, CH_2), 6.82 (s, 2H, NH_2), 7.62 (m, 2H, CH^{Ar}), 7.74 (m, 1H, CH^{Ar}), 8.06 (d, $J = 7.5$ Hz, 2H, CH^{Ar}), 8.20 (s, 1H, CH^{Pu}), 8.21 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 52.9$, 112.1, 128.3, 128.8, 134.0, 134.2, 146.8, 151.5, 152.1, 159.7, 193.4 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_{11}N_5NaO$ 276.08558, found 276.08648.

7-Benzyladenine (**10f**)
White solid; 0.120 g (90 %); m.p.: 231–234 °C (Ref. [48] 236–238 °C).

7-Allylpurine-2,6-diamine (**11b**, $C_8H_{10}N_6$)
White solid; 0.037 g (85 %); m.p.: 265 °C (decomp.); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.90$ (m, 3H, CH and CH_2), 5.16 (d, $J = 10.4$ Hz, 1H, CH), 5.51 (br s, 2H, NH_2), 6.00 (m, 1H, CH), 6.34 (br s, 2H, NH_2), 7.90 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 48.4$, 105.9, 116.9, 135.6, 145.0, 151.9, 160.5, 163.0 ppm; HRMS (ESI): *m/z* calcd for $C_8H_{10}N_6Na$ 213.08592, found 213.08630.

6-Methoxy-7-methyl-7H-purine (**12**, $C_7H_8N_4O$)
6-Chloro-7-methyl-7*H*-purine (0.20 g, 1.18 mmol) was added to a solution of 0.128 g MeONa (2.37 mmol) in 4 cm^3 of dry methanol. The resultant mixture was stirred for 3 h at ambient temperature and concentrated in vacuo. Flash chromatography (silica gel, ethyl acetate/methanol, 9:1) gave 0.19 g (91 %) of the title compound as white solid. M.p.: 179–182 °C (Ref. [49] 182–184 °C); NMR spectra in accordance with the literature data [49].

7-Benzyl-N-(triphenylphosphoranylidene)purine-6-amine (**13**, $C_{30}H_{24}N_5P$)
Triphenylphosphine (0.417 g, 1.59 mmol) was added to a solution of 0.20 g **8f** (0.80 mmol) in 6 cm^3 THF. The resultant mixture was stirred for 12 h at 60 °C and concentrated in vacuo. Column chromatography (silica gel, ethyl acetate/methanol, 9:1) afforded 0.370 g (95 %) of title compound as white solid. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 5.89$ (s, 2H, CH_2), 7.16 (m, 5H, CH^{Ar}), 7.36–7.46 (m, 9H, CH^{Ar}), 7.67 (m, 6H, CH^{Ar}), 7.87 (s, 1H, CH^{Pu}), 8.21 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 50.0$, 117.8, 118.1, 126.7, 127.4, 127.8, 128.2, 128.3, 128.4, 129.2, 131.80, 131.84, 132.7, 132.9, 137.6, 143.3, 152.6, 156.6, 156.7, 159.1 ppm.

7-Methyl-6-(morpholin-4-yl)purine (**14**, $C_{10}H_{13}N_5O$)
Dry acetonitrile (6 cm^3) was added to a mixture of 0.150 g 6-chloro-7-methyl-7*H*-purine (0.89 mmol) and 0.30 cm^3 morpholine (3.55 mmol). The resultant mixture was stirred for 3 h at 60 °C and concentrated in vacuo. Flash chromatography (silica gel, ethyl acetate/methanol, 9:1) gave 0.184 g (94 %) of the title compound as white solid. M.p.: 173–174 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 3.40$ (m, 4H, CH_2), 3.78 (m, 4H, CH_2), 3.99 (s, 3H, CH_3), 8.42 (s, 1H, CH^{Pu}), 8.49 (s, 1H, CH^{Pu}) ppm; ^{13}C NMR (125 Hz, DMSO-d_6): $\delta = 34.0$, 50.3, 65.8, 115.9, 148.2, 151.1, 154.7, 161.1 ppm; HRMS (ESI): *m/z* calcd for $C_{10}H_{13}N_5NaO$ 242.10123, found 242.10194.

Acknowledgments We are grateful for financial support from specific university research (MSMT No. 21/2012) and the Grant Agency of the Czech Republic (Grant No. 203/09/1552).

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