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Heck Reactions of 6- and 2-Halopurines

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Under the conditions of the Heck reaction, 9-benzyl-6-iodopurine affords mainly the corresponding 6,6′-dimer, the Heck product being formed only in low yield (≤12 %). With 7-benzyl-6-iodopurine the dimerization is suppressed and the Heck product is obtained in 32–91 % yield. 9-Substituted 6-chloro-2-iodopurines react smoothly, giving 2-alkenyl-6-chloropurines in 71–97 % isolated yields. The reaction proceeds with alkenes bearing electron-withdrawing substituents (like CO_2Bu, $COCH_3$, CN) and Ph, while vinyl acetate and dodec-1-ene are unreactive.

Introduction

Among a vast number of biologically active purine derivatives, alkenylpurines play an important role.[1] 6-Alkenylpurines, for example, are associated with antimycobacterial,[2] cytotoxic [3] and cytokinin[4] activity and with inhibition of 15-lipoxygenase.[5] Some 6-alkenylpurines have been designed as covalent analogues of DNA base pairs[6] or novel cross-linking agents,[7] and have also been used for the synthesis of fluorescent nucleoside analogues.[8] Moreover, 2-alkenyladenosine derivatives have been reported to function as inhibitors of adenosine receptors.[9]

Several methodologies have been used for the preparation of alkenylpurines. 6-Styrylpurine was first prepared by condensation of 6-methylpurine with benzaldehyde in the presence of HCl.[10] Another, more general, synthetic approach to 6-alkenylpurines, is based on Wittig reactions between 9-protected (purin-6-yl)methylene-triphenyl-λ^5-phosphanes (Wittig reagents) and aldehydes or ketones.[11] Cyclic 6-alkenyloxypurines have been prepared by intramolecular cyclization of 6-(hydroxyalkyn-1-yl)purines,[12] while 6-enaminopurines are accessible by addition of amines to 6-alkynylpurines.[13] Partial hydrogenation of 2-alkynyl-[14] and 8-alkynylpurines[15] to give the corresponding alkenes has also been reported. Hydrogenation of 6-alkynylpurines to 6-alkenylpurines was reported to proceed satisfactorily only with 9-unprotected bases, with overhydrogenation taking place otherwise.[4a] However, the most versatile methodology for the preparation of alkenylpurines – nowadays used almost without exception – is based on transition-metal-catalyzed cross-coupling reactions.[16] Alkenylpurines have thus been prepared by Pd-catalyzed reactions between halopurines or *O*-tosylpurines and alkenylstannanes,[17] alkenylzinc,[17c] or alkenylboron reagents.[18] An opposite approach, involving coupling of 2-stanylated purines with alkenyl halides, has also been described.[19] Heck reactions of 6-vinylpurines were reported to produce 6-alkenylpurines.[4a]

From this point of view it is interesting that Heck reactions starting from halopurines have not yet been reported, with the exception of the reaction between 8-bromocaffeine and *tert*-butyl acrylate.[20] Heck reactions of halopurines would be of key importance, since they would allow easy introduction of alkenes bearing EWG substituents such as CO_2R, CO, or CN, cases in which the corresponding alkenylstannanes and boronic acids are not commonly accessible. Recently, we have made attempts to perform Heck reactions on 6-halopurines, but without success. No reactions were observed under classical Heck conditions, whereas in the presence of Tl^I or Ag^I acetates the formation of N1-substituted hypoxanthine derivatives was observed.[21] When the reactions were run in the presence of hydride donors such as triethylammonium formate, saturated products of "reductive Heck reactions" were obtained.[22] Similarly, unsuccessful attempted vinylation of 6-halopurines with vinyl acetate under Heck conditions has been reported[4a]

Recently, as part of our continuing efforts to accomplish Heck reactions of 6- and 2-halopurines, we observed the formation of 6,6′-purine dimer **2** as a main product, but together with a small amount of the desired Heck product **3**, in the reaction between iodopurine **1** and butyl acrylate in the presence of palladium catalyst without phosphane ligand (Scheme 1).[23] Suppression of the dimerization could, thus, possibly open an avenue to Heck reactions of purine 6- and 2-halides. Purine dimers are highly polar compounds, and they could easily have evaded detection in previous research. Therefore, we reexamined the Heck reactions of 6- and 2-halopurines from this point of view.

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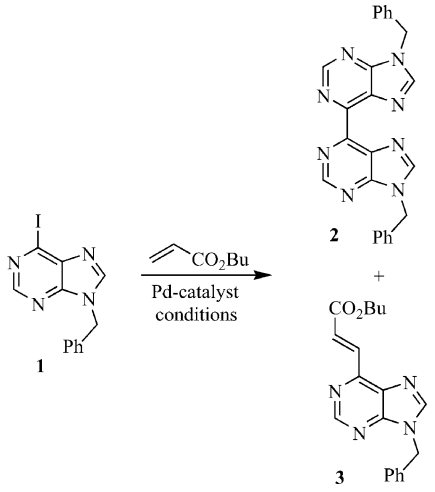
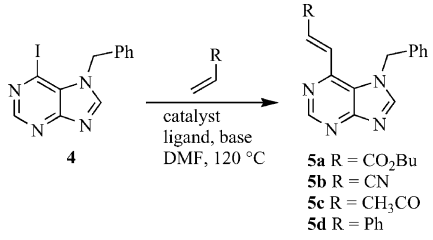


Scheme 1. Reaction between 9-benzyl-6-iodopurine and butyl acrylate under the conditions of the Heck reaction.

Results and Discussion

Repetition of the reaction between 9-benzyl-6-iodopurine (**1**) and butyl acrylate under the previously described conditions[21] confirmed that in the presence of $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ only decomposition of starting compounds takes place. However, when the reaction was performed under phosphane-free conditions the dimer **2** became the main product of the reaction, but accompanied by a small amount of the desired Heck reaction product **3** (Scheme 1). The reaction between **1** and butyl acrylate (4 equiv.) was then repeated in the presence of various bases (Et_3N, K_2CO_3, iPr$_2$NEt, Ag_2CO_3) and solvents (NMP, DMF, CH_3CN) at different temperatures and with $Pd(dba)_2$ or $Pd(OAc)_2$ as a source of palladium, with the aim of maximizing the formation of the Heck product. It appeared that the reaction requires polar solvent and a temperature above 100 °C, which excludes solvents such as THF, acetonitrile, or toluene. The best results were obtained in DMF at 120 °C; however, the yields of the Heck product **3** did not exceed 12%. The use of a large excess of butyl acrylate (56 equiv.) increased the yield only slightly, to 24%. The same result was obtained when the reaction was performed in an excess of butyl acrylate serving at the same time as solvent.

We next turned our attention to 7-benzyl-6-iodopurine (**4**), in the expectation that the formation of the corresponding 6,6′-dimer might be suppressed for steric reasons. Additionally, the reported lower reactivities of 6-halo-7-benzylpurines relative to their 9-benzyl analogues[17c] might be disadvantageous for the dimer formation. To our delight, the desired Heck product **5a** was obtained in 53% yield when the reaction was catalyzed by $Pd(OAc)_2$ in the presence of iPr$_2$NEt in DMF at 120 °C without phosphane ligand (Scheme 2, Table 1, Entry 1). To improve the yield, the reaction was further optimized. Similar result was obtained when $Pd(dba)_2$ was used instead of $Pd(OAc)_2$ (Table 1, Entry 2). In contrast, replacement of iPr$_2$NEt with K_2CO_3 or the use of $PdCl_2(PPh_3)_2$ as catalyst suppressed the reaction (Table 1, Entries 3 and 4). The yield increased to 77%, however, in the presence of 1.1 equiv. of Tl_2SO_4 (Table 1, Entry 5), while application of Na_3PO_4 as a base led to further improvement and the reaction under phosphane-free conditions gave **5a** in 89% yield. The combination of Na_3PO_4 with diPheCy$_2$P lowered the yield to 50% (Table 1, Entries 6 and 7), but a high yield of the Heck product was obtained when $Pd(OAc)_2$ was used in combination with diPheCy$_2$P and iPr$_2$NEt (Table 1, Entry 8). Since in this case the conversion of **4** was quantitative, which simplified separation of the product, these conditions were used for Heck reactions between **4** and other substrates. Under the above conditions, acrylonitrile, methyl vinyl ketone, and styrene



Scheme 2. Heck reactions of 7-benzyl-6-iodopurine.

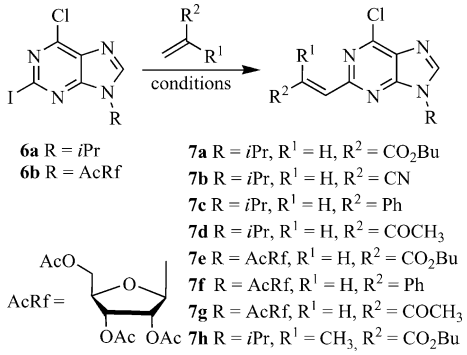
Table 1. Heck reactions of 7-benzyl-6-iodopurine (**4**, Scheme 2).[a]

Entry	R	Catalyst	Ligand	Base	% Yield[b]
1	CO_2Bu (**5a**)	$Pd(OAc)_2$	none	iPr$_2$NEt	53[c]
2	CO_2Bu (**5a**)	$Pd(dba)_2$	none	iPr$_2$NEt	51
3	CO_2Bu (**5a**)	$Pd(OAc)_2$	none	K_2CO_3	trace
4	CO_2Bu (**5a**)	$PdCl_2(PPh_3)_2$	none	iPr$_2$NEt	none
5	CO_2Bu (**5a**)	$Pd(OAc)_2$	none	iPr$_2$NEt	77[d]
6	CO_2Bu (**5a**)	$Pd(OAc)_2$	none	Na_3PO_4	89[c]
7	CO_2Bu (**5a**)	$Pd(OAc)_2$	diPheCy$_2$P	Na_3PO_4	50[c]
8	CO_2Bu (**5a**)	$Pd(OAc)_2$	diPheCy$_2$P	iPr$_2$NEt	86 (53[e])
9	CN (**5b**)	$Pd(OAc)_2$	diPheCy$_2$P	iPr$_2$NEt	49[e]
10	CH_3CO (**5c**)	$Pd(OAc)_2$	diPheCy$_2$P	iPr$_2$NEt	32[e]
11	Ph (**5d**)	$Pd(OAc)_2$	diPheCy$_2$P	iPr$_2$NEt	47[e]

[a] Reaction conditions: a mixture of **4** with alkene (4 equiv.), base (2 equiv.), catalyst (5 mol-%), and DiPheCy$_2$P (10 mol-%) in dry DMF (5 mL per mmol of **4**) was stirred under argon for 18 h at 120 °C. [b] The yields were established by ^{1}H NMR with 2,3,5-trinitrobenzene as internal standard. [c] Unreacted iodopurine **4** was present in the reaction mixture. [d] 1.1 Equiv. of Tl_2SO_4 was used as additive. [e] Isolated yield.

afforded the expected Heck-type products in fair yields (Table 1, Entries 9–11). In each case the (*E*) isomer of the product was obtained exclusively. Vinyl acetate, as an example of an electron-rich alkene, gave only a dehalogenation product – 7-benzylpurine. 6-Chloro-7-benzylpurine did not react under these conditions at all.

We also examined the Heck reactions of 6-chloro-2-iodo derivatives **6a** and **6b** (Scheme 3). Since the chlorine in the 6-position is not reactive, such reactions should selectively lead to the 2-alkenyl-6-chloro derivatives. In this case there is a possibility of further derivatization of such compounds at the 6-position giving biologically relevant compounds. The results are summarized in Table 2. As expected, the products were obtained with exclusive 2-selectivity, the reaction proceeding more easily than with 6-iododerivatives, and the dimerization did not occur. The reaction of **6a** was optimized with the respect to the source of palladium, the base used, the ligand, and the solvent. In DMF the yields obtained span the range from 51 to 88%; again, phosphane-free conditions and iPr$_2$NEt gave the best results (Entries 4, 8, 12, 13). Unlike the reactions with **1** and **4**, this reaction proceeds even in acetonitrile at 60 °C, giving the desired Heck product in 90% isolated yield after 3 h (Entry 15). Other less polar solvents such as THF, EtOAc, DCE, and toluene were less effective at this temperature, and only low levels of conversion of **6a** (2–9%) after prolonged reaction times were observed. To achieve acceptable reaction times with all substrates, acetonitrile as a solvent at 80 °C and Pd(dba)$_2$/iPr$_2$NEt were used for the reactions of **6a** and **6b** with other alkenes. Under these conditions, the reactions of both substrates with acrylonitrile, butyl acrylate, ethyl vinyl ketone, and styrene proceeded with high yields (Entries 18–23), but electron-rich substrates – vinyl acetate and dodec-1-ene – were unreactive. Only traces (≤3%) of the corresponding 2,2′-dimers were detected in the crude reaction mixtures under ligand-free conditions or when TFP or *o*-tolyl$_3$P were used as ligands. When the reactions were catalyzed with Pd(dba)$_2$/BipheCy$_2$P, formation of the 2,2′-dimer was not observed.



Scheme 3. Heck reactions of 6-chloro-2-iodopurine derivatives.

The sterically more demanding methyl methacrylate gave low conversion and a substantial amount of the dimer in the reaction with **6a** at 80 °C in acetonitrile. A higher reaction temperature was required in this case. However, even 3 d heating at 120 °C in DMF led only to 54% yield of the desired product **7h** (Table 2, Entry 23).

Table 2. Heck reactions of 2-iodopurines **6a** and **6b** (Scheme 3).[a]

Entry	R, R^1, R^2	Catalyst	Base	Solvent, temperature [°C]	% Yield[b]
1	iPr, H, CO$_2$Bu	Pd(OAc)$_2$	Na$_3$PO$_4$	DMF, 120	72
2	iPr, H, CO$_2$Bu	Pd(OAc)$_2$	K$_2$CO$_3$	DMF, 120	51
3	iPr, H, CO$_2$Bu	Pd(OAc)$_2$	Et$_3$N	DMF, 120	73
4	iPr, H, CO$_2$Bu	Pd(OAc)$_2$	iPr$_2$NEt	DMF, 120	79
5	iPr, H, CO$_2$Bu	Pd(PPh$_3$)$_4$	iPr$_2$NEt	DMF, 120	74
6	iPr, H, CO$_2$Bu	PdCl$_2$(PPh$_3$)$_2$	iPr$_2$NEt	DMF, 120	78
7	iPr, H, CO$_2$Bu	Pd(dba)$_2$	iPr$_2$NEt	DMF, 120	84
8	iPr, H, CO$_2$Bu	(C$_3$H$_5$PdCl)$_2$	iPr$_2$NEt	DMF, 120	79
9	iPr, H, CO$_2$Bu	Pd(dba)$_2$/TFP	iPr$_2$NEt	DMF, 120	54
10	iPr, H, CO$_2$Bu	Pd(dba)$_2$/*o*-tolyl$_3$P	iPr$_2$NEt	DMF, 120	73
11	iPr, H, CO$_2$Bu	Pd(dba)$_2$/BipheCy$_2$P	iPr$_2$NEt	DMF, 120	60
12	iPr, H, CO$_2$Bu	Pd(dba)$_2$	iPr$_2$NEt	DMF, 100	88
13	iPr, H, CO$_2$Bu	Pd(dba)$_2$	iPr$_2$NEt	DMF, 80	85
14	iPr, H, CO$_2$Bu	Pd(dba)$_2$	iPr$_2$NEt	MeCN, 80	85
15	iPr, H, CO$_2$Bu	Pd(dba)$_2$	iPr$_2$NEt	MeCN, 60	90
16	iPr, H, CO$_2$Bu	Pd(dba)$_2$	iPr$_2$NEt	MeCN, 40	40[c]
17	iPr, H, Ph	Pd(dba)$_2$	iPr$_2$NEt	MeCN, 80	87
18	iPr, H, CH$_3$CO	Pd(dba)$_2$	iPr$_2$NEt	MeCN, 80	97
19	iPr, H, CN	Pd(dba)$_2$	iPr$_2$NEt	MeCN, 80	80
20	AcRf, H, CO$_2$Bu	Pd(dba)$_2$	iPr$_2$NEt	MeCN, 80	71
21	AcRf, H, Ph	Pd(dba)$_2$	iPr$_2$NEt	MeCN, 80	78
22	AcRf, H, CH$_3$CO	Pd(dba)$_2$	iPr$_2$NEt	MeCN, 80	82
23	iPr, CH$_3$, CO$_2$Bu	Pd(dba)$_2$/BipheCy$_2$P	iPr$_2$NEt	DMF, 120[d]	54

[a] Reaction conditions: a mixture of **6a** or **6b** with alkene (4 equiv.), base (2 equiv.), and catalyst (5 mol-%) in the indicated solvent (5 mL per mmol of **6**) was stirred under argon under the indicated conditions for three hours. [b] Isolated yield. [c] Unreacted **6a** remains in the reaction mixture. [d] Reaction time was 3 d.

Conclusions

The Heck reactions of 9-substituted 6-iodopurines are complicated by competitive dimerization, the Heck products being formed only in low yields. When 7-substituted 6-iodopurine derivatives are used, however, the dimerization is suppressed and the products of the Heck reaction can be isolated in about 30–50% yields.[24] In contrast, the Heck reactions of 9-substituted 6-chloro-2-iodopurines proceed selectively at the 2-position, and the corresponding Heck products are formed smoothly in high yields, accompanied by only trace amounts of 2,2′-dimers. In most cases a catalytic system without phosphane ligand using $Pd(dba)_2$ [or a combination of $Pd(dba)_2$ with biPheCy$_2$P] and *i*Pr$_2$NEt as a base gave the best results.[25]

Experimental Section

General: All reactions were performed under nitrogen. NMR spectra were measured on a Varian Gemini 300 (^{1}H, 300.07 MHz; ^{13}C, 75.46 MHz), a Bruker AMX3 400 (^{1}H, 400.13 MHz and ^{13}C, 100.62 MHz) or a Bruker DRX 500 Avance (^{1}H, 500.13 MHz and ^{13}C, 125.77 MHz) spectrometer at 298 K. Unambiguous assignment of the NMR signals is based on ^{13}C{^{1}H}, ^{13}C APT, COSY, HMQC and ^{13}C HMBC spectra. IR spectra were recorded on a Nicolet 750 FT-IR instrument. Mass spectra were measured on a ZAB-SEQ (VG Analytical) machine. The solvents were dried and degassed by standard procedures; silica gel (ICN SiliTech, 32–63) was used for column chromatography. 9-Benzyl-6-iodopurine[26] (**1**), 7-benzyl-6-iodopurine[17c] (**4**), 9-benzyl-6-chloropurine,[3] 6-chloro-2-iodo-9-isopropylpurine[27] (**6a**), and 6-chloro-2-iodo-9-(*O*,*O*,*O*-triacetyl-β-D-ribofuranosyl)purine[28] (**6b**) were prepared by the reported procedures; other compounds were purchased.

Butyl 3-(9-Benzylpurine-6-yl)acrylate (3): Dry DMF (0.5 mL), then butyl acrylate (2 mL, 14 mmol) and *i*Pr$_2$NEt (65 mg, 0.5 mmol) were added under argon to a mixture of 9-benzyl-6-iodopurine (**1**, 84 mg, 0.25 mmol) and $Pd(dba)_2$ (7 mg, 0.0125 mmol). The resulting mixture was then stirred at 120 °C for 18 h, silica (5 g) was added, volatiles were evaporated, and flash chromatography with EtOAc/hexane (2:1) afforded **3** (20 mg, 24%) as a colorless solid; m.p. 59–62 °C. ^{1}H NMR ($CDCl_3$): δ = 0.95 (t, J = 7.3 Hz, 3 H, CH_3), 1.42 (m, 2 H, CH_2), 1.70 (m, 2 H, CH_2), 4.24 (t, J = 6.5 Hz, 2 H, O–CH_2), 5.46 (s, 2 H, CH_2), 7.33 (m, 5 H, ArH), 7.62 (d, J = 16.0 Hz, 1 H, =CH), 8.1 (s, 1 H, 8-H), 8.1 (d, J = 16.0 Hz, 1 H, =CH), 9.0 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.7, 19.1, 30.6, 47.4, 64.8, 127.8, 128.7, 129.2, 132.0, 134.8, 138.0, 145.2, 151.1, 152.5, 152.6, 166.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2962, 1713, 1583, 1496, 1454, 1403, 1326, 1299, 1278 cm^{-1}. HR MS (EI): calculated for $C_{19}H_{20}N_4O_2$: 336.1586; found 336.1561.

The corresponding-6,6′-dimer **2** is not eluted under these conditions and was not isolated. The presence of **6** in large amounts in the crude reaction mixture could, however, be shown by ^{1}H NMR [($CDCl_3$, 300 MHz): δ = 5.54 (s, 4 H, CH_2Ph), 7.36 (br. s, 10 H, ArH), 8.23 (s, 2 H, H-8), 9.31 (s, 2 H, H-2) ppm.[23]

General Procedure for Heck Reactions of 7-Benzyl-6-iodopurine (4): Dry DMF (3 mL), then the alkene (1 mmol) and *i*Pr$_2$NEt (65 mg, 0.5 mmol) were added under argon to a mixture of 7-benzyl-6-iodopurine (**4**, 84 mg, 0.25 mmol), $Pd(OAc)_2$ (3 mg, 0.0125 mmol), and DiPheCy$_2$P (9 mg, 0.025 mmol). The resulting mixture was stirred at 120 °C for 18 h, silica (5 g) was added, volatiles were evaporated, and the product was obtained by flash chromatography.

Butyl 3-(7-Benzylpurine-6-yl)acrylate (5a): Purification of the crude reaction mixture by flash chromatography with ethyl acetate/methanol (20:1) gave the desired product **5a** (45 mg, 54%) as a yellow solid; m.p. 95–97 °C. ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, J = 7.3 Hz, CH_3, 3 H), 1.38 (m, 2 H, CH_2), 1.66 (m, 2 H, CH_2), 4.19 (t, J = 6.4 Hz, 2 H, CH_2O), 5.62 (s, 2 H, CH_2Ph), 7.13 (m, 2 H, ArH), 7.20 (d, J = 15 Hz, 1 H, =CH), 7.35 (m, 3 H, ArH), 7.86 (d, J = 15 Hz, 1 H, =CH), 8.31 (s, 1 H, 8-H), 9.08 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.6, 19.1, 30.6, 51.7, 64.9, 123.0, 126.5, 127.7, 129.0, 129.4, 133.8, 135.7, 144.6, 149.8, 153.2, 162.9, 165.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2962, 2934, 1713, 1582, 1562, 1487, 1453, 1389, 1369, 1336, 1302, 1284, 1158, 970 cm^{-1}. HR MS (EI): calculated for $C_{19}H_{20}N_4O_2$: 336.1586; found 336.1599.

3-(7-Benzylpurine-6-yl)acrylonitrile (5b): Chromatography with EtOAc/methanol (20:1) gave **5b** (32 mg, 49%) as a yellow solid; m.p. 96–98 °C. ^{1}H NMR ($CDCl_3$): δ = 5.63 (s, 2 H, CH_2), 6.85 (d, J = 15.5 Hz, 1 H, =CH), 7.09 (m, 2 H, ArH), 7.39 (m, 3 H, ArH), 7.51 (d, J = 15.5 Hz, 1 H, =CH), 8.34 (s, 1 H, 8-H), 9.05 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 51.6, 116.9, 122.4, 126.2, 129.3, 129.7, 133.5, 141.6, 142.3, 150.5, 153.0, 163.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2224, 1580, 1562, 1488, 1451, 1391, 1369, 1335, 1165, 952 cm^{-1}. HR MS (EI): calculated for $C_{15}H_{19}ClN_4O_2$: 261.1014; found 261.1010.

7-Benzyl-6-(3-oxobut-1-enyl)purine (5c): Chromatography with EtOAc/methanol (9:1) gave **5c** (22 mg, 32%) as a yellow solid; m.p. 145–150 °C. ^{1}H NMR ($CDCl_3$): δ = 2.3 (s, 3 H, MeCO), 5.65 (s, 2 H, CH_2Ph), 7.14 (d, J = 7.7 Hz, 2 H, ArH), 7.37 (m, 3 H, ArH), 7.53 (d, J = 15.1 Hz, 1 H, CH=), 7.68 (d, J = 15.1 Hz, 1 H, CH=), 8.35 (s, 1 H, 8-H), 9.12 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.4, 51.7, 123.5, 126.4, 129.0, 129.5, 133.5, 133.6, 133.8, 144.8, 150.0, 153.2, 163.0, 197.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1695, 1580, 1488, 1455, 1368, 1335 cm^{-1}. HR MS (EI): calculated for $C_{16}H_{14}N_4O$ 278.1168; found 278.1176.

7-Benzyl-6-(2-phenylethenyl)purine (5d):[29] Chromatography with EtOAc/methanol (9:1) gave **5d** (37 mg, 47%) as a yellow solid; m.p. 179–182 °C. ^{1}H NMR ($CDCl_3$): δ = 5.67 (s, 2 H, CH_2Ph), 7.15 (m, 3 H, 2H ArH and 1H CH=), 7.41 (m, 8 H, ArH), 8.23 (d, J = 14.6 Hz, 1 H, CH=), 8.32 (s, 1 H, 8-H), 9.09 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 51.5, 120.2, 122.2, 125.9, 127.7, 128.7, 128.8, 129.5, 134.9, 135.5, 138.8, 147.7, 149.2, 153.2, 162.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1631, 1582, 1558, 1487, 1455, 1370 cm^{-1}. HR MS (EI): calculated for $C_{20}H_{16}N_4$ 312.1375; found 312.1352.

General Procedure for Heck Reactions of 6-Chloro-2-iodopurines 6a and 6b: Dry DMF or acetonitrile (3 mL per 0.25 mmol of iodopurine), then the alkene (4 equiv.) and *i*Pr$_2$NEt$_2$ (2 equiv.) were added under argon to a mixture of **6a** or **6b** (1 equiv.) and $Pd(dba)_2$ (0.05 equiv.). The resulting mixture was stirred for 3 h at the temperature given in Table 2. Silica (5 g) was added, volatiles were evaporated, and a pure product was obtained by flash chromatography.

Butyl 3-(6-Chloro-9-isopropylpurine-2-yl)acrylate (7a): Use of the General Procedure starting from **6a** (81 mg, 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.0125 mmol), butyl acrylate (128 mg, 1 mmol), and *i*Pr$_2$NEt (65 mg, 0.5 mmol), with heating at 60 °C in dry acetonitrile (3 mL) and chromatography with EtOAc/hexane (2:1), gave **7a** (73 mg, 90%) as a yellow solid; m.p. 69–74 °C. ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, J = 7.4 Hz, 3 H, CH_3), 1.46 (m, 2 H, CH_2), 1.69 (d, J = 6.8 Hz, 6 H, CH_3), 1.74 (m, 2 H, CH_2), 4.25 (t, J = 6.6 Hz, 2 H, O–CH_2), 4.95 (m, 1 H, *CH*Me$_2$), 7.26 (d, J = 15.7 Hz, 1 H, =CH), 7.73 (d, J = 15.7 Hz, 1 H, =CH), 8.19 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.7, 19.2, 22.5, 30.7, 48.3, 64. 8, 127.4, 131.3, 141.8, 143.8, 150. 8, 151.8, 156.5, 166.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2964, 2937,

2877, 1714, 1652, 1588, 1555, 1487, 1460, 1426, 1392, 1298, 1283, 1250, 1171 cm^{-1}. HR MS (EI): calculated for $C_{15}H_{19}ClN_4O_2$ 322.1197; found 322.1199.

3-(6-Chloro-9-isopropylpurine-2-yl)acrylonitrile (7b): Use of the General Procedure starting from **6a** (162 mg, 0.5 mmol), $Pd(dba)_2$ (14 mg, 0.025 mmol), acrylonitrile (106 mg, 2 mmol), and iPr_2NEt (130 mg, 1 mmol), with heating at 120 °C in dry DMF (6 mL) and chromatography with EtOAc/hexane (2:1), afforded **7b** 99 mg (80%) as a yellow solid; m.p. 185–190 °C. ^1H NMR ($CDCl_3$): δ = 1.69 (d, J = 6.8 Hz, 6 H, CH_3), 4.94 (m, 1 H, $CHMe_2$), 6.85 (d, J = 16.1 Hz, 1 H, =CH), 7.51 (d, J = 16.2 Hz, 1 H, =CH), 8.23 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.5, 48.4, 105.6, 117.1, 131.8, 144.3, 147.8, 151.1, 151.7, 154.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2226, 1586, 1553, 1485, 1461, 1390, 1340, 1322, 1173, 1147, 967, 917 cm^{-1}. HR MS (EI): calculated for $C_{11}H_{10}ClN_5$ 247.0625; found 247.0628.

6-Chloro-9-isopropyl-2-(2-phenylethenyl)purine (7c): Use of the General Procedure starting from **6a** (81 mg, 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.0125 mmol), styrene (104 mg, 1 mmol), and iPr_2NEt (65 mg, 0.5 mmol), with heating at 80 °C in dry acetonitrile (3 mL) and chromatography with EtOAc/hexane (2:1), gave **7c** (65 mg, 87%) as a yellow solid; m.p. 147–149 °C. ^1H NMR ($CDCl_3$): δ = 1.69 (d, J = 6.8 Hz, 6 H, CH_3), 4.98 (m, 1 H, $CHMe_2$), 7.29 (d, J = 15.7 Hz, 1 H, =CH), 7.35 (m, 1 H, ArH), 7.41 (m, 2 H, ArH), 7.65 (d, J = 7.4 Hz, 2 H, ArH), 8.04 (d, J = 15.9 Hz, 1 H, =CH), 8.13 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.6, 47.8, 126.6, 127.6, 128.8, 129.1, 130.1, 136.0, 138.2, 142.7, 150.5, 152.0, 159.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2931, 2857, 1639, 1591, 1551, 1495, 1454, 1425, 1388, 1344, 1323, 1281 cm^{-1}. HR MS (EI): calculated for $C_{16}H_{15}ClN_4$ 298.0985; found: 298.0981.

6-Chloro-9-isopropyl-2-(3-oxobut-1-enyl)purine (7d): Use of the General Procedure starting from **6a** (81 mg, 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.0125 mmol), methyl vinyl ketone (70 mg, 1 mmol), and iPr_2NEt (65 mg, 0.5 mmol), with stirring at 80 °C in dry acetonitrile (3 mL) and chromatography with EtOAc/hexane (2:1), afforded **7d** (64 mg, 97%) as a yellow solid; m.p. 183–187 °C. ^1H NMR ($CDCl_3$): δ = 1.69 (d, J = 6.8 Hz, 6 H, CH_3), 2.46 (s, 3 H, $COCH_3$), 4.95 (m, 1 H, $CHMe_2$), 7.44 (d, J = 16.0 Hz, 1 H, =CH), 7.57 (d, J = 16.0 Hz, 1 H, =CH), 8.21 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.5, 27.8, 48.4, 131.4, 134.8, 140.6, 144.0, 150.8, 151.9, 156.7, 198.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3051, 1677, 1628, 1588, 1554, 1424, 1389, 1266 cm^{-1}. HR MS (EI): calculated for $C_{12}H_{13}ClN_4O$ 264.0778; found 264.0772.

Butyl [6-Chloro-9-(*O*-triacetyl-β-D-ribofuranosyl)purine-2-yl]acrylate (7e): Use of the General Procedure starting from **6b** (180 mg, 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.0125 mmol), acrylonitrile (128 mg, 1 mmol), and iPr_2NEt (65 mg, 0.5 mmol), with heating at 80 °C in dry acetonitrile (3 mL) and chromatography with EtOAc/hexane (2:1), gave **7e** (127 mg, 94%) as a white foam. ^1H NMR ($CDCl_3$): δ = 0.98 (t, J = 7.4 Hz, 3 H, CH_3), 1.46 (m, 2 H, CH_2), 1.70 (m, 2 H, CH_2), 2.10 (s, 6 H, $COCH_3$), 2.19 (s, 3 H, $COCH_3$), 4.25 (t, J = 6.6 Hz, 2 H, O–CH_2), 4.38 (dd, J_1 = 4.1, J_2 = 12.4 Hz, 1 H, CH_2O), 4.45 (dd, J_1 = 2.9, J_2 = 12.3 Hz, 1 H, CH_2OAc), 4.5 (m, 1 H, CH), 5.68 (t, J = 5.2 Hz, 1 H, AcO–CH), 5.92 (t, J = 5.2 Hz, 1 H, AcO–CH), 6.24 (d, J = 4.9 Hz, 1 H, O–CH), 7.27 (d, J = 15.7 Hz, 1 H, =CH), 7.72 (d, J = 15.7 Hz, 1 H, =CH), 8.31 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.7, 19.2, 20.4, 20.5, 20.7, 30.7, 62.8, 64.9, 70.3, 73.3, 80.4, 86.7, 128.3, 131.5, 141.2, 144.1, 151.5, 151.6, 157.4, 166.1, 169.3, 169.5, 170.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2964, 2937, 1753, 1715, 1591, 1557, 1390, 1298, 1284, 1171 cm^{-1}. HR MS (EI): calculated for $C_{23}H_{27}ClN_4O_9$ 538.1467; found 538.1489.

6-Chloro-2-(2-phenylethenyl)-9-(*O*-triacetyl-β-D-ribofuranosyl)-purine (7f): Use of the General Procedure starting from **6b** (159 mg, 0.30 mmol), $Pd(dba)_2$ (6 mg, 0.011 mmol), styrene (125 mg, 1.2 mmol), and iPr_2NEt (78 mg, 0.6 mmol), with heating at 80 °C in dry acetonitrile (3 mL) and chromatography with EtOAc/hexane (2:1), gave **7f** (120 mg, 78%) as a white foam. ^1H NMR ($CDCl_3$): δ = 2.05 (s, 3 H, $COCH_3$), 2.14 (s, 3 H, $COCH_3$), 2.20 (s, 3 H, $COCH_3$), 4.37 (dd, J_1 = 5.1, J_2 = 13.1 Hz, 1 H, CH_2OAc), 4.49 (m, 2 H, 1H CH and 1H CH_2OAc), 5.89 (t, J = 5.5 Hz, 1 H, AcO–CH), 6.09 (t, J = 4.6 Hz, 1 H, AcO–CH), 6.20 (d, J = 4.4 Hz, 1 H, O–CH), 7.30 (d, J = 16.0 Hz, 1 H, =CH), 7.37 (m, 1 H, ArH), 7.42 (m, 2 H, ArH), 7.69 (d, J = 7.3 Hz, 2 H, ArH), 8.10 (d, J = 16.0 Hz, 1 H, =CH), 8.20 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.4, 20.6, 20.7, 62.6, 70.1, 73.2, 80.1, 87.2, 126.0, 127.8, 128.8, 129.3, 130.4, 135.8, 139.3, 143.5, 151.2, 151.7, 160.1, 69.4, 169.5, 170.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3051, 1752, 1594, 1554, 1498, 1452, 1390, 1266 cm^{-1}. HR MS (EI): calculated for $C_{24}H_{23}ClN_4O_7$ 514.1255; found 514.1277.

6-Chloro-2-(3-oxobut-2-enyl)-9-(*O*-triacetyl-β-D-ribofuranosyl)-purine (7g): Use of the General Procedure starting from **6b** (159 mg, 0.30 mmol), $Pd(dba)_2$ (9 mg, 0.015 mmol), methyl vinyl ketone (84 mg, 1.2 mmol), and iPr_2NEt (78 mg, 0.6 mmol), with heating at 80 °C in dry acetonitrile (3 mL) and chromatography with EtOAc/hexane (2:1), afforded **7g** (119 mg, 82%) as a white foam. ^1H NMR ($CDCl_3$): δ = 2.09 (s, 3 H, $COCH_3$), 2.11 (s, 3 H, $COCH_3$), 2.19 (s, 3 H, $COCH_3$), 2.47 (s, 3 H, $COCH_3$), 4.36–4.52 (m, 3 H, 2H CH_2OAc and 1H CH), 5.73 (t, J = 5.5 Hz, 1 H, AcO–CH), 6.09 (t, J = 5.1 Hz, 1 H, AcO–CH), 6.23 (d, J = 4.5 Hz, 1 H, O–CH), 7.49 (d, J = 16.0 Hz, 1 H, =CH), 7.57 (d, J = 16.0 Hz, 1 H, =CH), 8.32 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.4, 20.5, 20.7, 28.0, 62.8, 70.3, 73.2, 80.3, 86.9, 131.6, 135.4, 139.8, 144.4, 151.5, 151.6, 157.6, 169.3, 169.5, 170.2, 198.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1753, 1678, 1557, 1390, 1368, 1266, 1226 cm^{-1}. HR MS (EI): calculated for $C_{20}H_{21}ClN_4O_8$ 480.1048; found 480.1057.

Methyl 3-(6-Chloro-9-isopropylpurine-2-yl)methacrylate (7h): Dry DMF (3 mL), then methyl methacrylate (100 mg,1 mmol) and iPr_2NEt (65 mg, 0.5 mmol) were added under argon to a mixture of **6a** (81 mg, 0.25 mmol), $Pd(dba)_2$ (7 mg, 0.0125 mmol) and Di-PheCy$_2$P (9 mg, 0.025 mmol). The resulting mixture was stirred at 120 °C for 3 d. Purification by flash chromatography with EtOAc/hexane (2:1) gave **9** (38 mg, 54%) as a bright yellow oil. ^1H NMR ($CDCl_3$): δ = 1.69 (d, J = 6.8 Hz, 6 H, CH_3), 2.53 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 4.91 (m, 1 H, $CHMe_2$), 7.74 (s, 1 H, =CH), 8.19 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.5, 22.4, 48.4, 52.3, 130.2, 135.2, 136.5, 143.8, 150.2, 151.5, 157.8, 168.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2955, 2856, 1714, 1590, 1554, 1489, 1460, 1438, 1393, 1378, 1345, 1277, 1172, 1145, 1122 cm^{-1}. HR MS (EI): calculated for $C_{13}H_{15}ClN_4O_2$ 294.0884; found 294.0888.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **3**, **5a**–**d**, and **7a**–**h**.

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[1] For review on biological activities displayed by purines see: M. Legraverend, D. S. Grierson, *Bioorg. Med. Chem.* **2006**, *14*, 3987–4006.
[2] A. K. Bakkestuen, L.-L. Gundersen, G. Langli, F. Liu, J. M. J. Nolsøe, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1207–1210.
[3] A. Bråthe, L.-L. Gundersen, J. Nissen-Meyer, F. Rise, B. Spilsberg, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 877–880.
[4] a) A. Bråthe, L.-L. Gundersen, F. Rise, A. B. Eriksen, A. V. Vollsnes, L. Wang, *Tetrahedron* **1999**, *55*, 211–228; b) A. Bråthe, L.-L. Gundersen, F. Rise, A. B. Eriksen, *J. Plant Growth Regul.* **2005**, *24*, 41–45.
[5] A. Bråthe, G. Andresen, L.-L. Gundersen, K. E. Malterud, F. Rise, *Bioorg. Med. Chem.* **2002**, *10*, 1581–1586.
[6] a) M. Hocek, I. Votruba, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1055–1058; b) M. Hocek, H. Dvořáková, I. Císařová, *Collect. Czech. Chem. Comun.* **2002**, *67*, 1560–1578.
[7] F. Nagatsugi, K. Uemura, S. Nakashima, M. Maeda, S. Sasaki, *Tetrahedron* **1997**, *53*, 3035–3044.
[8] W. M. Odijk, G. J. Koomen, *Tetrahedron* **1985**, *41*, 1893–1904.
[9] S. Vittori, E. Camaioni, E. Di Francesco, R. Volpini, A. Monopoli, S. Dionisotti, E. Ongini, G. Cristalli, *J. Med. Chem.* **1996**, *39*, 4211–4217.
[10] A. Hampton, *J. Heterocycl. Chem.* **1974**, *11*, 255–256.
[11] E. C. Taylor, S. F. Martin, *J. Am. Chem. Soc.* **1974**, *96*, 8095–8102.
[12] T. Ch. Berg, L.-L. Gundersen, A. B. Eriksen, K. E. Malterud, *Eur. J. Org. Chem.* **2005**, 4988–4994.
[13] M. Kuchař, R. Pohl, I. Votruba, M. Hocek, *Eur. J. Org. Chem.* **2006**, 5083–5098.
[14] A. Matsuda, M. Shinozaki, Y. Toyofumi, H. Homma, R. Nomoto, T. Miyasaka, Y. Watanabe, T. Abiru, *J. Med. Chem.* **1992**, *35*, 241–252.
[15] G. Sági, L. Ötvös, S. Ikeda, G. Andrei, R. Snoeck, E. De Clercq, *J. Med. Chem.* **1994**, *37*, 1307–1311.
[16] For a recent review see: M. Hocek, *Eur. J. Org. Chem.* **2003**, 245–254.
[17] See for instance: a) A. A. Van Aerschot, P. Mamos, N. J. Weyns, S. Ikeda, E. De Clercq, P. A. Herdewijn, *J. Med. Chem.* **1993**, *36*, 2938–2942; b) L.-L. Gundersen, *Tetrahedron Lett.* **1994**, *35*, 3155–3158; c) L.-L. Gundersen, A. K. Bakkestuen, A. J. Aasen, H. Øveras, F. Rise, *Tetrahedron* **1994**, *50*, 9743–9756; d) F. Nagatsugi, K. Uemura, S. Nakashima, M. Maeda, S. Sasaki, *Tetrahedron Lett.* **1995**, *36*, 421–424.
[18] a) M. Havelková, M. Hocek, M. Česnek, D. Dvořák, *Synlett* **1999**, 1145–1147; b) M. Havelková, D. Dvořák, M. Hocek, *Synthesis* **2001**, 1704 –1710; c) F. Berrée, P. G.-L. Bleis, B. Carboni, *Tetrahedron Lett.* **2002**, *43*, 4935–4938.
[19] a) K. Kato, H. Hayakawa, H. Tanaka, H. Kumamoto, S. Shindoh, S. Shuto, T. Miyasaka, *J. Org. Chem.* **1997**, *62*, 6833–6841; b) K. Kato, H. Hayakawa, H. Tanaka, H. Kumamoto, T. Miyasaka, *Tetrahedron Lett.* **1995**, *36*, 6507–6510.
[20] K. A. Jacobson, D. Shi, C. Gallo-Rodriguez, M. Manning, C. Müller, J. W. Daly, J. L. Meumayer, L. Kiriasis, W. Pfleiderer, *J. Med. Chem.* **1993**, *36*, 2639–2644.
[21] M. Havelková, M. Studenovský, D. Dvořák, *Collect. Czech. Chem. Commun.* **2000**, *65*, 797–804.
[22] T. Tobrman, D. Dvořák, *Tetrahedron Lett.* **2004**, *45*, 273–276.
[23] T. Tobrman, D. Dvořák, *Collect. Czech. Chem. Commun.* **2007**, *72*, 1365–1374.
[24] A study to determine whether the higher yield of the Heck product in the case of 7-benzyl-6-iodopurine is a result of the steric hindrance of the benzyl group or due to the different electronic distribution in 7-benzyl-6-iodopurine is now being undertaken in our laboratory.
[25] Interestingly, only traces of the corresponding Heck product were detected if the used reaction conditions were applied in the reactions between 6-chloro-8-iodo-9-isopropylpurine and butyl acrylate or styrene. Optimization of the reaction conditions to achieve Heck reactions of 8-halopurines will thus require further study.
[26] T. C. McKenzie, J. W. Epstein, *J. Org. Chem.* **1982**, *47*, 4881–4884.
[27] M. Legraverend, O. Ludwig, E. Bisagni, S. Leclerc, L. Meijer, N. Giocanti, R. Sadri, V. Favaudon, *Bioorg. Med. Chem.* **1999**, *7*, 1281–1293.
[28] V. Nair, S. G. Richardson, *Synthesis* **1982**, 670–672.
[29] Compound **5d** was reported in connection with its biological activity (A. Bråthe, L.-L. Gundersen, K. E. Malterud, F. Rise, *Arch. Pharm. Chem. Life Sci.* **2005**, *338*, 159–166) with a ref.[2] to its preparation. However, ref.[2] does not mention compound **5d**.

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