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'Reductive Heck reaction' of 6-halopurines

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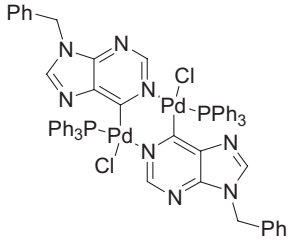
Abstract—Alkenylation of 9-benzyl-6-halopurines with alkenes does not proceed under conventional Heck conditions. However, in the presence of triethylammonium formate a mixture of the corresponding saturated products was obtained. In contrast to the classical Heck reaction, the regioselectivity of this process is low giving a mixture of both α- and β-products regardless of the electronic nature of the substituent on the double bond of the alkene.

The Heck reaction, a Pd-catalyzed coupling reaction of sp^2-halides (or triflates) with olefins, has become an indispensable tool for organic synthesis.[1] Numerous applications of this methodology have been described in the field of heterocyclic chemistry.[2] Somewhat surprisingly, this reaction has not been successfully used for derivatization of purines. Such a reaction would make functionalized alkenyl purines with a wide range of biological effects like cytokinin activity,[3] activity against *Mycobacterium tuberculosis*[4] and antioxidant activity easily accessible.[5] However, to the best of our knowledge, the reaction of 8-bromocaffeine with *tert*-butyl acrylate is the only example of this type to have appeared in the literature.[6] Interestingly, the opposite approach, reactions of 6-vinylpurine with organohalides were successful.[3]

We have recently attempted to perform the Heck reaction of 6-halo-9-benzylpurines with activated alkenes like butyl acrylate and acrylonitrile, however, the reaction did not proceed in any case, and the starting purine derivatives remained unreacted. However, in the presence of TlOAc or AgOAc, *N*′-substituted hypoxanthine derivatives were obtained.[7] Lack of reactivity of 6-halopurines in the Heck reaction is unexpected, since other Pd-catalyzed reactions, for example, Stille[8a,b] or Suzuki[8c,d] couplings, proceeded smoothly.[8e,f] Examples of low reactivity of 2-haloazines in the Heck reaction, have been reported[9a,b] and were explained by the formation of a stable dimer[9a] of the product of oxidative addition.[10] In the case of 9-benzyl-6-chloropurine the corresponding dimer **1** was isolated and characterized.[11] It was shown, that **1** reacts with tributylphenyltin giving



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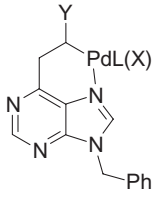
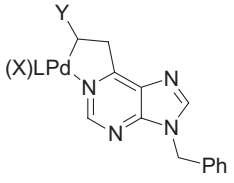


2a



2b

Keywords: Heck reaction; Alkylpurine; Pd-catalysis.
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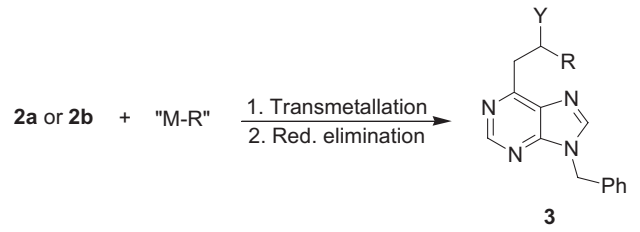


Scheme 1.

the product of Stille coupling and might therefore be an intermediate for Stille reactions of 6-halopurines.[11] Another process which would exclude palladium from the catalytic cycle might be the formation of a stable chelate either with N7 **2a** or N1 **2b**,[12] after alkene insertion.

In the latter case, reaction with an appropriate transmetallating reagent might result in the formation of saturated derivatives **3** via transmetallation and reductive elimination (Scheme 1). Herein we report on our attempts to use this approach for the preparation of 6-alkylpurine derivatives.

Reaction of 9-benzyl-6-iodopurine **4a**[8b] with butyl acrylate **5a** under the conditions of the Heck reaction ($Pd(PPh_3)_2Cl_2$, DMF, Et_3N) in the presence of phenylboronic acid and phenyltributyltin was unsuccessful.[13] However, when the same conditions were applied but in the presence of sodium formate, a mixture of the saturated products **3a** and **6a** in an approximately 1:1 ratio was obtained in 47% overall yield (Table 1, entry 1). With triethylammonium formate formed in situ the ratio **3a** to **6a** reached 1:2 in 75% overall yield (Scheme 2, Table 1, entry 2).

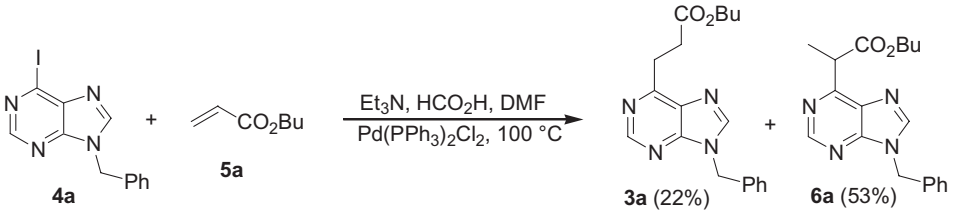
Reaction in acetonitrile gave similar results to DMF (Table 1, entry 3). A significant effect of the phosphine ligand on the course of reaction was observed. While $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ and $Pd(OAc)_2/PPh_3$ (2 equiv) in DMF gave almost identical results (Table 1, entries 3–5), the combination of $Pd(OAc)_2$ and $P(OPh)_3$ (Table 1, entry 6) or P(2-furyl)$_3$ (Table 1, entry 7) gave lower overall yields. A mixture of $Pd(OAc)_2$ with the more electron donating $P(Cy)_3$ (Table 1, entry 8), chelating dppp (Table 1, entry 9) as well as $Pd(OAc)_2$ without phosphine ligand (Table 1, entry 10) gave only the product of dehydrohalogenation. In contrast to other ligands, 2-(dicyclohexylphosphino)biphenyl gave **3a** as the main product (Table 1, entry 11). 9-Benzyl-6-chloropurine **4b**[8b] reacted like iodopurine **4a**, however, the reaction was slower (Table 1, entry 12). 7-Benzyl-6-iodopurine **4c**[8b] gave exclusively the product of dehalogenation (Table 1, entry 13).

Table 1. Reaction of 6-halopurines with butyl acrylate **5a**[a] (Scheme 2)

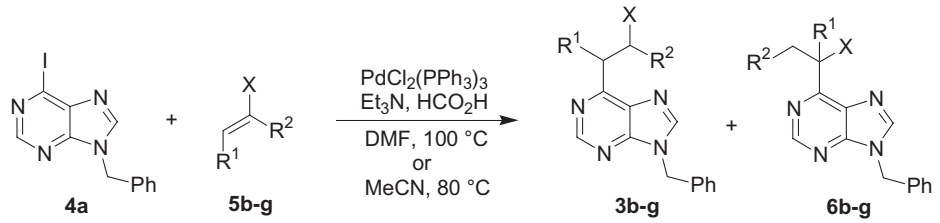
Entry	Halopurine	Catalyst	Product (% yield)[b]
1	**4a**	$Pd(PPh_3)_2Cl_2$[c]	**3a** (22)
			6a (25)
2	**4a**	$Pd(PPh_3)_2Cl_2$	**3a** (22)
			6a (53)
3	**4a**	$Pd(PPh_3)_2Cl_2$[d]	**3a** (25)
			6a (48)
4	**4a**	$Pd(PPh_3)_4$	**3a** (25)
			6a (54)
5	**4a**	$Pd(OAc)_2$, PPh_3[e]	**3a** (26)
			6a (50)
6	**4a**	$Pd(OAc)_2$, $P(OPh)_3$[e]	**3a** (15)
			6a (24)
7	**4a**	$Pd(OAc)_2$, P(2-furyl)$_3$[e]	**3a** (10)
			6a (17)
8	**4a**	$Pd(OAc)_2$, $P(Cy)_3$[e]	Traces of **3a** and **6a**[f]
9	**4a**	$Pd(OAc)_2$, dppp[g]	—[f]
10	**4a**	$Pd(OAc)_2$	—[f]
11	**4a**	$Pd(OAc)_2$	**3a** (35)
		P(2-biphenyl)Cy_2[e]	**6a** (15)
12	**4b**	$Pd(PPh_3)_2Cl_2$	**3a** (27)
			6a (46)
13	**4c**	$Pd(PPh_3)_2Cl_2$	—[f]

[a] Reaction conditions: 5 mol% of Pd, 4 equiv of alkene, 8 equiv Et_3N, 6 equiv HCO_2H, DMF, 100 °C.
[b] Isolated yield.
[c] HCO_2Na was used instead of HCO_2H.
[d] Reaction in CH_3CN at 80 °C.
[e] Pd/phosphine 1:2.
[f] Almost complete dehalogenation was observed.
[g] Pd/dppp 1:1.

$PdCl_2(PPh_3)_2$ was used as the catalyst in the reaction with other substrates (Scheme 3).[14] While substitution of the double bond in its α-position resulted in a substantial reduction in yield (methyl methacrylate **5b**, Table 2, entry 1), introduction of a methyl group at the β-position (methyl crotonate **5c**, Table 2, entry 2) led mainly to dehalogenated product. Among other electron acceptor substituted alkenes, methyl vinyl ketone **5d** produced only the β-substituted product in a fair yield (Table 2, entry 3), while reaction of acrylonitrile **5e** was more complicated. Besides the expected products **3e** and **6e**, the product of Michael addition of **6e** to acrylonitrile **7** was formed (Table 2, entry 4). Evidently, the strong electron deficiency of the purine nucleus taken together



Scheme 2.



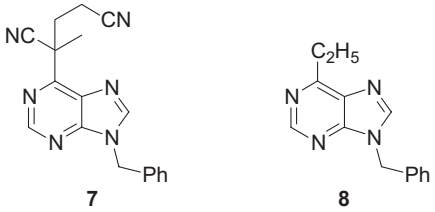
Scheme 3.

Table 2. Reaction of 9-benzyl-6-iodopurine **4a** with alkenes[a] (Scheme 3)

Entry	Alkene	Product (% yield)[b]
1	**5b** $X = CO_2CH_3$; $R^1 = H$; $R^2 = CH_3$	**3b** (16) **6b** (9)
2	**5c** $X = CO_2CH_3$; $R^1 = CH_3$; $R^2 = H$	9-Benzylpurine (80)
3	**5d** $X = COCH_3$; $R^1 = R^2 = H$	**3d** (34)[c] **3d** (25)[c,d]
4	**5e** $X = CN$; $R^1 = R^2 = H$	**3e** (22) **6e** (23) **7** (30)
5	**5f** $X = Ph$; $R^1 = R^2 = H$	**3f** (24) **6f** (27)
6	**5g** $X = OAc$; $R^1 = R^2 = H$	**6g** (29) **8** (12)

[a] Reaction conditions: 5 mol % of Pd, 4 equiv of alkene, 8 equiv Et_3N, 6 equiv HCO_2H, DMF, 100 °C.
[b] Isolated yield.
[c] NMR yield.
[d] Reaction in acetonitrile at 80 °C.

with the nitrile group of **6e** makes the α-hydrogen in **6e** acidic enough to be deprotonated by triethylamine. Styrene **5f** reacted smoothly giving 51% of a mixture of both linear **3f** and branched **6f** products in an approximately 1:1 ratio (Table 2, entry 5). When vinyl acetate **5g**, as an example of an electron rich alkene, was used, the starting purine **4a** was consumed in less then 1 h and α-substituted product **6g** was formed accompanied by 9-benzyl-6-ethylpurine **8** (Table 2, entry 6).[15]



The compounds prepared were tested for cytostatic activity by evaluating their in vitro inhibition of cell growth in mouse leukaemia L1210 cells (ATCC CCL 219); human promyelocytic leukaemia HL60 cells (ATCC CCL 240); human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2) and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119). None of the compounds tested showed any significant activity.

In conclusion, 6-halopurines react with terminal alkenes under the conditions of the Heck reaction in the presence of formate giving saturated analogues of the expected Heck reaction products.[16] In contrast to the usual outcome of Heck reactions, regioselectivity in this process is low, and a mixture of linear and branched products was formed in most cases. Despite the relatively low yields and selectivity this reaction allows rapid access to purine derivatives that are not easily accessible by other methods. The scope and mechanistic aspects of this reaction as well as other activity tests are now under study in our laboratory.

Acknowledgements

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13. With phenyltributyltin, the product of Stille coupling (9-benzyl-6-phenylpurine) was formed, while no reaction took place with phenylboronic acid.
14. Representative procedure: To a mixture of **4a** (168 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol) and PPh_3 (13 mg, 0.05 mmol), degassed DMF (3 mL) was added under argon. Then **5a** (0.29 mL, 2 mmol), Et_3N (0.55 mL, 4 mmol) and HCO_2H (0.11 mL, 3 mmol) was successively added via syringe and the mixture was stirred for 1 h at 100 °C. During this time all starting **4a** disappeared (TLC). The solvent was then evaporated in vacuum and the residue chromatographed on silica. Elution with heptane/ethyl acetate 1:2 gave **6a** (84 mg, 50%) and further elution with ethyl acetate/methanol 9:1 afforded **3a** (44 mg, 26%). **3a**: White amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, $J = 7.4$ Hz, 3H, CH_3), 1.32 (m, 2H, CH_2CH_3), 1.57 (m, 2H, $CH_2CH_2CH_3$), 3.00 (t, $J = 7.4$ Hz, 2H, $PuCH_2CH_2CO$), 3.55 (t, $J = 7.4$ Hz, 2H, $PuCH_2CH_2CO$), 4.08 (t, $J = 6.6$ Hz, 2H, $CO_2CH_2CH_2$ CH_2), 5.44 (s, 2H, CH_2Ph), 7.28–7.40 (m, 5H, PhH), 8.01 (s, 1H, H-8), 8.90 (s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6 (CH_3), 19.0 (CH_2CH_3), 27.8 ($PuCH_2$ CH_2CO), 30.6 ($CH_2CH_2CH_3$), 31.5 ($PuCH_2CH_2CO$), 47.3 (CH_2Ph), 64.4 ($OCH_2CH_2CH_2CH_3$), 127.8 (CH-Ph), 128.6 (CH-Ph), 129.1 (CH-Ph), 132.4 (C5-Pu), 135.1 (C-Ph), 143.6 (C8-Pu), 150.7 (C4-Pu), 152.5 (C2-Pu), 160.6 (C6-Pu), 172.3 (CO_2Bu); IR ($CHCl_3$) 3021, 2965, 1730, 1596, 1499, 1407, 1333, 1209, 1190, 699 cm^{-1}. HR-MS (EI) calcd for $C_{19}H_{22}N_4O_2$ 338.1743, found 338.1736. **6a**: White amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.20 (m, 2H, CH_2CH_3), 1.52 (m, 2H, $CH_2CH_2CH_3$), 1.69 (d, $J = 7.1$ Hz, 3H, $CHCH_3$), 4.12 (t, $J = 6.3$ Hz, 2H, CO_2CH_2 CH_2CH_2), 4.59 (q, $J = 7.1$ Hz, 1H, $CHCH_3$), 5.44 (s, 2H, CH_2Ph), 7.29–7.38 (m, 5H, PhH), 8.03 (s, 1H, H-8), 8.95 (s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.0 (CH_2CH_3), 15.9 ($CHCH_3$), 18.9 (CH_2CH_3), 30.4 ($CH_2CH_2CH_2CH_3$), 43.3 ($CHCH_3$), 47.3 (CH_2Ph), 65.0 ($OCH_2CH_2CH_2CH_3$), 127.9 (CH-Ph), 128.6 (CH-Ph), 129.1 (CH-Ph), 131.9 (C5-Pu), 135.0 (C-Ph), 144.0 (C8-Pu), 151.3 (C4-Pu), 152.7 (C2-Pu), 160.0 (C6-Pu), 172.3 (CO_2Bu); IR ($CHCl_3$) 2991, 2964, 1734, 1594, 1500, 1457, 1406, 1333, 1208, 1196 cm^{-1}. HR-MS (EI) calcd for $C_{19}H_{22}N_4O_2$ 338.1743, found 338.1735.
15. Formation of the ethyl derivative **8** remains unclear. Acetoxy derivative **6g** is not an intermediate, since it is stable under the conditions used. In our opinion, the most probable way for the formation of **8** involves formation of a 6-vinylpurine derivative by β-elimination of acetate from the product of insertion of vinyl acetate. The ethyl derivative is then formed by Pd-catalyzed transfer hydrogenation of the vinyl group.
16. 2-Bromopyridine, in accordance with Ref. 9a, did not react with butyl acrylate under 'classical' Heck conditions. Addition of HCO_2H led to the formation of the product analogous to **3a**, but the yield was very low (8%).