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ORIGINAL PAPER

# Palladium-catalysed Claisen rearrangement of 6-allyloxypurines

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*Dedicated to Professor Štefan Toma on the occasion of his 75th birthday*

6-Allyloxypurines readily undergo palladium-catalysed Claisen rearrangement under mild conditions affording $N^1$-substituted hypoxanthines. In contrast with the previously reported protocol, the Claisen rearrangement can be performed using $Pd(PPh_3)_4$ or $Pd(dba)_2$/dppf in dry THF at 60 °C. The reaction can accommodate variously substituted allyl fragments to position $N^1$ of the hypoxanthine skeleton with high yields. Retention of the double bond configuration during rearrangement was observed.


**Keywords:** Claisen rearrangement, purine, allyloxypurines, palladium, hypoxanthine

## Introduction

Purine derivatives occur extensively in biological systems as the components of nucleic acids. It is not surprising, therefore, that many substituted purines are biologically active compounds displaying, for example, antiviral (Simons et al., 2005; De Clercq & Neyts, 2004), anti-fungal (Miura & Izuta, 2004; Szafraniec et al., 2004), or anti-neoplastic (Lagoja, 2005; Kimura & Bugg, 2003; Rachakonda & Cartee, 2004) properties. Recent reports of artificially modified nucleosides make possible the investigation of the structure and function of RNAs (Phelps et al., 2012). The introduction of alkyne chain into RNA is frequently used for further functionalisation of RNAs by azide/alkyne cycloaddition (Yamada et al., 2011). Even very simple naturally occurring substituted purines are biologically active. Thus, theophylline and theobromine are used as anti-asthma drugs (Wieland & Bauer, 1951), 1,3-dimethylisoguanine shows activity against human ovarian cancer (Mitchell et al., 1997), and 1-methylherbipoline acts as an inhibitor of collagenase (Yagi et al., 1994). In addition, purine acts as a copper corrosion inhibitor in both alkaline and neutral sulfate solutions (Petrović et al., 2012).

## Experimental

All reactions were performed in an argon atmosphere. $^1$H (300.07 MHz or 600.13 MHz) and $^{13}$C (75.45 MHz or 150.90 MHz) NMR spectra were measured on Varian Gemini 300 or Bruker Avance III 600 instruments, respectively. IR spectra (neat samples) were recorded on a Nicolet 6700 with continuum microscope. 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 stereochemical purity of commercially available crotyl alcohol was 95 % *E*. Other compounds were commercially available products and alkenes were used as ≥ 98 % *E* isomers. Preparation of compounds: *Ia*, *Ig*, *IIa*, and *IIg* was reported previously (Ranganathan et al., 1986).

### *General method for preparation of starting 6-allyloxypurines I*

Corresponding alcohol (2 mmol) was added to a suspension of NaH (2 mmol, 80 mg, 60 % suspen-

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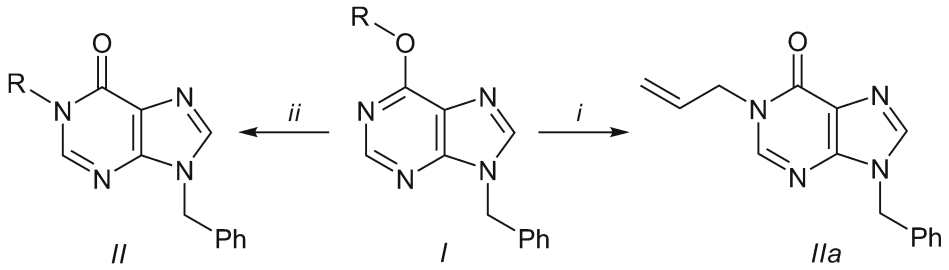


**Fig. 1.** Claisen rearrangement of various 6-allyloxy-9-benzyl-9*H*-purines (*Ia–If*) and 9-benzyl-6-(prop-2-ynyloxy)-9*H*-purine (*Ig*) to corresponding 1-allyl-9-benzylhypoxanthines (*IIa–IIf*) and 9-benzyl-1-(prop-2-ynyl)hypoxanthine (*IIg*), respectively. Reaction conditions: *i*) see Table 1 for optimised reaction conditions for rearrangement of 6-allyloxy-9-benzyl-9*H*-purine (*I*, R = allyloxy) to 1-allyl-9-benzylhypoxanthine (*IIa*); *ii*) for rearrangement of *Ib–Ig* to corresponding *IIb–IIg*: $Pd(PPh_3)_4$ or $Pd(dba)_2$/dppf, THF, 60 °C, 16 h.

**Table 1.** Optimisation of transition metal catalysed rearrangement of 6-allyloxy-9-benzyl-9*H*-purine (*Ia*) to 1-allyl-9-benzylhypoxanthine (*IIa*)

| Entry | Catalyst[a] | Solvent | Temperature/ °C | Yield[b]/% |
|---|---|---|---|---|
| 1 | Hoveyda–Grubbs 2 | toluene | 110 | 60 |
| 2 | $Cu(acac)_2$ | toluene | 110 | 65 |
| 3 | $Ru(PPh_3)_2Cl_2$ | toluene | 110 | 55 |
| 4 | $Rh(PPh_3)_2Cl$ | toluene | 110 | 45 |
| 5 | $Pd(PPh_3)_2Cl_2$ | toluene | 100 | 64 |
| 6 | $Pd(PPh_3)_4$ | toluene | rt | 58 |
| 7 | $Pd(PPh_3)_4$ | DCM | rt | 77 |
| 8 | $Pd(PPh_3)_4$ | THF | rt | 91 |
| 9 | $Pd(dba)_2$/dppf[c] | THF | rt | 96 |
| 10 | $Pd(dba)_2$/TFP[d] | THF | rt | 77 |

*a*) 5 mole % of catalyst was used; *b*) isolated yield of *IIa*; *c*) 5 mole % of dppf was used; *d*) 10 mole % of TFP was used; rt – ambient temperature.

sion in mineral oil) in dry THF (5 mL) and the mixture was stirred for 30 min at ambient temperature, followed by the addition of 9-benzyl-6-chloro-9*H*-purine (1 mmol, 245 mg) or 9-benzyl-6-chloro-2-iodo-9*H*-purine (1 mmol, 371 mg), or 9-benzyl-6-methoxy-8-iodo-9*H*-purine (1 mmol, 366 mg). The mixture was stirred at 60 °C for 16 h, pre-concentrated at reduced pressure and the crude products were purified by column chromatography (silica gel, hexane/EtOAc, $\varphi_r$ = 1 : 2) to give the final products *Ia–Ii*.

### *General method for Claisen rearrangement of Ia–Ii*

A solution of allyloxypurine *I* (1 mmol) and $Pd(PPh_3)_4$ (5 mole %, 0.05 mmol, 58 mg) or $Pd(dba)_2$ (5 mole %, 0.05 mmol, 29 mg), or dppf (5 mole %, 0.05 mmol, 28 mg) in dry THF (5 mL) was stirred at 60 °C for 16 h. The solvent was evaporated at reduced pressure and the crude product was purified by flash chromatography (silica gel, EtOAc/MeOH, $\varphi_r$ = 20 : 1) to afford the corresponding hypoxanthine *II*.

## Results and discussion

As a part of our on-going effort to develop a new selective synthesis of biologically active purines (Tobrman & Dvořák, 2003, 2008; Kotek et al., 2010, 2012), we focused on the cross-metathesis of alkenyl purines. This area of purine chemistry remains almost untouched (Vik & Gundersen, 2007). However, to our surprise, when 6-allyloxypurine *Ia* was heated to 110 °C in dry toluene in the presence of second generation Hoveyda–Grubbs catalyst, formal product of Claisen rearrangement *IIa* was isolated with 60 % yield instead of the anticipated product of self-metathesis (Fig. 1, Table 1, entry 1). The thermal Claisen rearrangement of *Ia* has already been described as proceeding at 190 °C to afford 30 % yield (Ranganathan et al., 1986). As many transition metals are known to catalyse this kind of rearrangement (Schenck & Bosnich, 1985; Castro, 2004), we tested several of them. While $Ni(acac)_2$, $Co(acac)_2$, and $Cr(acac)_3$ were inactive, $Cu(acac)_2$, $Ru(PPh_3)_2Cl_2$, $Rh(PPh_3)_2Cl$, and all Pd complexes catalysed this reaction (Table 1, entries 1–5). None of these complexes with the exception of $Pd(PPh_3)_4$ (Table 1, entry 6) worked below 100 °C. Running the same reaction in dry dichloromethane (DCM) increased the yield of *IIa* to 77 % (Table 1, entry 7) and the best result (91 % yield) was obtained when THF was used as a solvent (Table 1, entry 8). A some-

**Table 2.** Palladium-catalysed Claisen rearrangement of various 6-allyloxy-9-benzyl-9*H*-purines (*Ia–If*) and 9-benzyl-6-(prop-2-ynyloxy)-9*H*-purine (*Ig*)

| Entry | Series | Purine *I* | Hypoxanthine *II* | Yield[a]/% |
|---|---|---|---|---|
| | | R | R | |
| 1 | a | $CH_2$═$CHCH_2$ | $CH_2$═$CHCH_2$ | 96[b] |
| 2 | b | Cyclohex-2-enyl | Cyclohex-2-enyl | 82[b] |
| 3 | c | (*E*)-PhCH═$CHCH_2$ | (*E*)-PhCH═$CHCH_2$ | 98[c] |
| 4 | d | Geranyl | Geranyl | 84[b] (39[d], 61[e])[c] |
| 5 | e | (*E*)-$CH_3CH$═$CHCH_2$[f] | (*E*)-$CH_3CH$═$CHCH_2$[g] | 89[h] |
| 6 | f | $CH_2$═$CHCHCH_3$ | $CH_2$═$CHCHCH_3$ | – |
| 7 | g | CH≡$CCH_2$ | $CH_2$═C═CH | 65[i,j], 25[i] |

*a*) Isolated yield of *II* (product of rearrangement); *b*) using 5 mole % of $Pd(dba)_2$/dppf as catalyst; *c*) using 5 mole % of $Pd(PPh_3)_4$ as catalyst; *d*) yield of stereoisomers of *IId*; *e*) yield of 9-benzyl-6-hypoxanthine; *f*) 95 % of *E*-isomer (determined by $^1$H NMR); *g*) 80 % of *E*-isomer (determined by $^1$H NMR); *h*) overall isolated yield of the mixture of *IIe* and *IIf* in the ratio of 58 : 42; *i*) using 5 mole % of $PdCl_2(PPh_3)_2$ as catalyst; *j*) the yield determined by $^1$H NMR of crude reaction mixture (durene was used as internal standard).

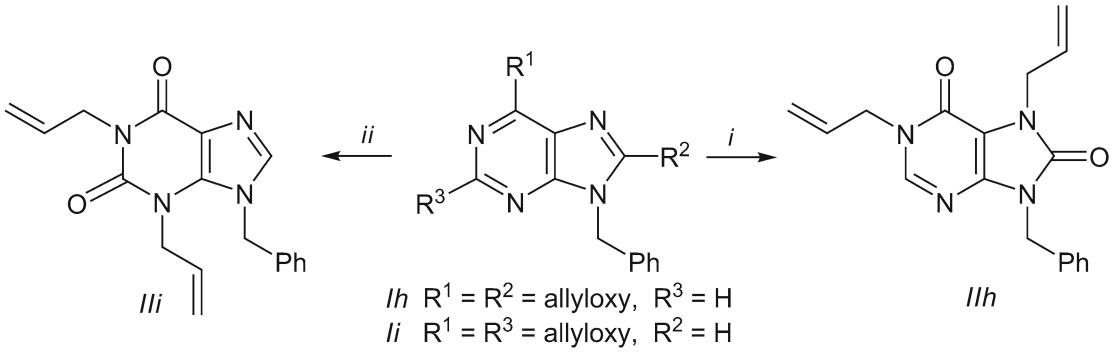


**Fig. 2.** Claisen rearrangement of bisallyloxypurines *Ih* and *Ii*. Reaction conditions: *i*) *Ih*, 5 mole % of $Pd(dba)_2$/dppf, THF, 60 °C, 16 h, 93 % yield of *IIh*; *ii*) *Ii*, 5 mole % of $Pd(dba)_2$/dppf, THF, 60 °C, 16 h, 87 % yield of *IIi*.

what higher yield was obtained using $Pd(dba)_2$/dppf in THF, while $Pd(dba)_2$/TFP gave a yield comparable with $Pd(PPh_3)_4$ (Table 1, entries 9, 10).

The optimised reaction conditions (Table 1, entries 8 or 9) were applied to the rearrangement of various 6-allyloxypurines *Ib–If* and also 9-benzyl-6-(prop-2-ynyloxy)-9*H*-purine (*Ig*) (Fig. 1, Table 2). In contrast with the rearrangement of *Ia*, heating of the reaction mixtures to 60 °C was needed to achieve a complete conversion of the starting purines *Ib–Ig*. Thus, 6-(cyclohex-3-enyloxy)purine *Ib* was smoothly converted to the hypoxanthine *IIb* using $Pd(dba)_2$/dppf and the cinnamyloxypurine *Ic* was transformed exclusively to the corresponding (*E*)-1-(3-phenylprop-2-enyl)hypoxanthine (*IIc*) affording a 98 % yield in the presence of $Pd(PPh_3)_4$ (Table 2, entries 2 and 3). The outcome of the isomerisation of the geranyloxy derivative *Id* was dependent on the phosphine ligand used. With $Pd(dba)_2$/dppf, clean conversion to only (*E*)-1-geranylhypoxanthine (*IId*) with 84 % yield was observed. By contrast, isomerisation of *Id* performed in the presence of $Pd(PPh_3)_4$ afforded a mixture of the rearranged product *IId* with 39 % isolated yield along with 9-benzylhypoxanthine with 61 % yield (Table 2, entry 4). In the case of the isomeric purines *Ie* and *If* bearing (*E*)-6-(but-2-enyloxy) or 6-(1-methylallyloxy) moieties, both conditions including $Pd(PPh_3)_4$, or $Pd(dba)_2$/dppf afforded inseparable mixture of isomeric products *IIe* and *IIf* at the same 58 : 42 ratio and 89 % overall isolated yield (Table 2, entries 5 and 6). In all the cases reported in Table 2, the formation of small amounts (< 5 %) of 9-benzylhypoxanthine was observed. The only exception was the rearrangement of *IId* in the presence of $Pd(PPh_3)_4$ referred to above, where 9-benzylhypoxanthine was the main product.

We also tested the ability of the readily available 6,8- and 2,6-bisallyloxy-9-benzylpurines *Ih* and *Ii*, respectively to undergo the above isomerisation. The starting compounds *Ih* and *Ii* are available by double nucleophilic displacement of 9-benzyl-8-iodo-6-methoxy-9*H*-purine and 9-benzyl-6-chloro-2-iodo-9*H*-purine with allyl alcohol in the presence of NaH in dry THF. In the first case, not only iodine but also the methoxy group in position 6 is substituted. Subsequent isomerisation of *Ih*, and *Ii* using $Pd(dba)_2$/dppf in dry THF at 60 °C readily afforded the products of the double Claisen rearrangement with high yields (Fig. 2).

**Table 3.** Physical and spectral data of 6-allyloxypurines *I* and hypoxanthines *II*

| Compound | Physical and spectral data[a] |
|---|---|
| *Ib* | M.p. 82–85 °C<br>$^1$H NMR (300 MHz, $CDCl_3$), $\delta$: 1.8–2.1 (m, 6H, $CH_2$), 5.40 (s, 2H, $CH_2$), 5.90 (m, 1H, CH), 5.98 (s, 2H, CH), 7.30 (m, 5H, CH″), 7.86 (s, 1H, CH′), 8.54 (s, 1H, CH′)<br>$^{13}$C NMR (75.5 MHz, $CDCl_3$), $\delta$: 18.9, 25.0, 28.3, 47.3, 70.6, 121.5, 125.7, 127.7, 128.4, 129.0, 132.8, 135.4, 141.7, 152.20, 152.25, 160.6<br>HRMS (ESI), $m/z$ (found/calc.): 329.13742/329.13728 ($C_{18}H_{18}N_4ONa$) |
| *Ic* | M.p. 124–127 °C<br>$^1$H NMR (300 MHz, $CDCl_3$), $\delta$: 5.29 (d, $J = 6.0$ Hz, 2H, $CH_2$), 5.42 (s, 1H, $CH_2$), 6.54 (td, $J = 6.0$ Hz, $J = 15.8$ Hz, 1H, =CH), 6.81 (d, $J = 15.8$ Hz, 1H, =CH), 7.26–7.40 (m, 10H, CH″), 7.90 (s, 1H, CH′), 8.59 (s, 1H, CH′)<br>$^{13}$C NMR (75.5 MHz, $CDCl_3$), $\delta$: 47.4, 67.4, 123.5, 126.6, 127.7, 127.9, 128.3, 128.4, 128.5, 129.0, 134.2, 135.2, 136.3, 142.0, 152.1, 152.2, 160.4.<br>HRMS (ESI), $m/z$ (found/calc.): 365.13741/365.13728 ($C_{21}H_{18}N_4ONa$) |
| *Id* | M.p. 67–72 °C<br>$^1$H NMR (300 MHz, $CDCl_3$), $\delta$: 1.59 (s, 3H, $CH_3$), 1.65 (s, 3H, $CH_3$), 1.79 (s, 3H, $CH_3$), 2.10 (m, 4H, $CH_2$), 5.08 (t, $J = 6.6$ Hz, 1H, CH), 5.14 (d, $J = 7.2$ Hz, 2H, $CH_2$), 5.41 (s, 2H, $CH_2$), 5.62 (t, $J = 6.3$ Hz, 1H, CH), 7.27–7.37 (m, 5H, CH″), 7.87 (s, 1H, CH′), 8.56 (s, 1H, CH′)<br>$^{13}$C NMR (75.5 MHz, $CDCl_3$), $\delta$: 16.6, 17.5, 25.5, 26.1, 39.4, 47.2, 63.8, 118.5, 121.3, 123.7, 127.6, 128.3, 128.9, 131.6, 135.3, 141.7, 142.0, 152.0, 152.1, 160.7<br>HRMS (ESI), $m/z$ (found/calc.): 385.20007/385.19988 ($C_{22}H_{26}N_4ONa$) |
| *Ie*[b] | $^1$H NMR (300 MHz, $CDCl_3$), $\delta$: 1.72 (d, $J = 5.7$ Hz, 3H, $CH_3$), 5.03 (d, $J = 5.4$ Hz, 2H, $CH_2$), 5.39 (s, 2H, $CH_2$), 5.90 (m, 2H, CH), 7.24–7.34 (m, 5H, CH″), 7.87 (s, 1H, CH′), 8.54 (s, 1H, CH′)<br>$^{13}$C NMR (75.5 MHz, $CDCl_3$), $\delta$: 17.7, 47.3, 67.6, 121.4, 125.3, 127.7, 128.4, 129.0, 131.5, 135.3, 152.16, 152.18, 160.6<br>HRMS (ESI), $m/z$ (found/calc.): 303.12169/303.12163 ($C_{16}H_{16}N_4ONa$) |
| *If* | $^1$H NMR (300 MHz, $CDCl_3$), $\delta$: 1.52 (d, $J = 5.7$ Hz, 3H, $CH_3$), 5.14 (d, $J = 9.6$ Hz, 2H, $CH_2$), 5.33 (m, 3H, $CH_2$ and CH), 6.00 (m, 2H, CH), 7.25 (m, 5H, CH″), 7.86 (s, 1H, CH′), 8.51 (s, 1H, CH′)<br>$^{13}$C NMR (75.5 MHz, $CDCl_3$), $\delta$: 20.1, 47.2, 73.3, 115.9, 121.4, 127.6, 128.3, 128.9, 135.2, 137.7, 152.17, 152.28, 160.2<br>HRMS (ESI), $m/z$ (found/calc.): 303.12177/303.12163 ($C_{16}H_{16}N_4ONa$) |
| *Ih* | $^1$H NMR (300 MHz, $CDCl_3$), $\delta$: 4.91 (d, $J = 5.7$ Hz, 2H, $CH_2$), 5.07 (d, $J = 6.6$ Hz, 2H, $CH_2$), 5.30 (m, 4H), 5.40 (m, 2H, CH), 6.20 (m, 2H, =CH), 7.30 (m, 5H, CH″), 7.71 (s, 1H, CH′)<br>HRMS (ESI), $m/z$ (found/calc.): 345.13235/345.13220 ($C_{18}H_{18}N_4O_2Na$) |
| *Ii* | $^1$H NMR (300 MHz, $CDCl_3$), $\delta$: 5.09 (m, 4H, $CH_2$), 5.24 (s, 2H, $CH_2$), 5.35 (m, 4H, $=CH_2$), 6.10 (m, 2H, =CH), 7.30 (m, 5H, CH″), 8.41 (s, 1H, CH′)<br>HRMS (ESI), $m/z$ (found/calc.): 345.13241/345.13220 ($C_{18}H_{18}N_4O_2Na$) |
| *IIb* | M.p. 129–136 °C<br>$^1$H NMR (300 MHz, $CDCl_3$), $\delta$: 1.60 (m, 2H, $CH_2$), 2.05 (m, 4H, $CH_2$), 5.25 (s, 2H, $CH_2$), 5.55 (m, 2H, CH), 6.10 (m, 1H, CH), 7.25 (m, 5H, CH″), 7.72 (s, 1H, CH′), 8.03 (s, 1H, CH′)<br>$^{13}$C NMR (75.5 MHz, $CDCl_3$), $\delta$: 19.1, 24.3, 30.0, 47.1, 49.3, 123.7, 125.3, 127.4, 128.1, 128.7, 134.1, 135.2, 139.6, 145.3, 147.3, 156.2<br>IR (neat), $\tilde{\nu}$/cm$^{-1}$: 3099, 3035, 2929, 1679, 1570, 1544, 1507, 1496, 1449, 1424, 1358, 1229, 1204, 1184, 1130, 1064, 960, 929, 873, 787, 737, 717, 696, 677, 656<br>HRMS (ESI), $m/z$ (found/calc.): 329.13727/329.13728 ($C_{18}H_{18}N_4ONa$) |
| *IIc* | M.p. 197–205 °C<br>$^1$H NMR (300 MHz, $CDCl_3$), $\delta$: 4.84 (d, $J = 6.9$ Hz, 2H, $CH_2$), 5.31 (s, 2H, $CH_2$), 6.35 (td, $J = 6.6$ Hz, $J = 15.8$ Hz, 1H, =CH), 6.62 (d, $J = 15.8$ Hz, 1H, =CH), 7.25–7.37 (m, 10H, CH″), 7.75 (s, 1H, CH′), 8.05 (s, 1H, CH′)<br>$^{13}$C NMR (75.5 MHz, $CDCl_3$), $\delta$: 47.4, 47.9, 123.3, 126.5, 127.6, 128.2, 128.5, 128.6, 129.0, 134.4, 135.2, 135.7, 139.8, 146.8, 155.8.<br>IR, $\tilde{\nu}$/cm$^{-1}$: 3100, 3035, 2993, 2927, 2853, 1680, 1606, 1573, 1543, 1508, 1494, 1454, 1439, 1429, 1351, 1305, 1269, 1223, 1200, 1178, 1140, 1080, 1051, 1028, 978, 960, 861, 847, 789, 740, 723, 688, 669, 653<br>HRMS (ESI), $m/z$ (found/calc.): 365.13745/365.13728 ($C_{21}H_{18}N_4ONa$) |
| *IId* | M.p. 140–144 °C<br>$^1$H NMR (300 MHz, $CDCl_3$), $\delta$: 1.56 (s, 3H, $CH_3$), 1.64 (s, 3H, $CH_3$), 1.78 (s, 3H, $CH_3$), 2.05 (m 4H, $CH_2$), 4.66 (d, $J = 7.2$ Hz, 2H, $CH_2$), 5.03 (m, 1H, =CH), 5.29 (s, 2H, $CH_2$), 5.32 (m, 1H, =CH), 7.20–7.35 (m, 5H, CH″), 7.72 (s, 1H, CH′), 7.96 (s, 1H, CH′)<br>$^{13}$C NMR (75.5 MHz, $CDCl_3$), $\delta$: 16.4, 17.6, 25.6, 26.1, 39.4, 43.3, 47.3, 118.3, 123.4, 124.2, 127.6, 128.4, 129.0, 132.0, 135.3, 139.7, 142.3, 146.6, 147.6, 156.6<br>IR, $\tilde{\nu}$/cm$^{-1}$: 3101, 3040, 2971, 2917, 2850, 1674, 1571, 1545, 1509, 1495, 1453, 1438, 1376, 1361, 1345, 1306, 1280, 1226, 1199, 1172, 1135, 1078, 1052, 1028, 970, 941, 875, 860, 847, 802, 790, 761, 723, 694, 652<br>HRMS (ESI), $m/z$ (found/calc.): 385.19998/385.19988 ($C_{22}H_{26}N_4ONa$) |

**Table 3.** (continued)

| Compound | Physical and spectral data[a] |
|---|---|
| *IIe*, *IIf*[c] | $^1$H NMR (600 MHz, $CDCl_3$), $\delta$: 1.54 (d, $J$ = 6.0 Hz, $CH_3$), 1.72 (d, $J$ = 6.0 Hz, $CH_3$), 1.83 (d, $J$ = 6.0 Hz, $CH_3$), 4.63 (d, $J$ = 6.0 Hz, $CH_2$), 4.74 (d, $J$ = 6.0 Hz, $CH_2$), 5.31 (s, $CH_2$), 5.35 (m, CH), 5.55 (m, CH), 5.65 (m, CH), 5.75–5.85 (m, CH), 6.05 (m, CH), 7.25 (m, CH″), 7.74 (s, CH′), 7.96, 7.98, 7.99 (s, CH′)<br>$^{13}$C NMR (75.5 MHz, $CDCl_3$), $\delta$: 12.7, 17.3, 18.7, 41.9, 47.2, 49.6, 49.9, 117.4, 123.6, 123.8, 123.9, 124.9, 127.3, 127.9, 128.5, 129.4, 130.4, 135.1, 136.9, 139.5, 139.6, 144.7, 146.4, 146.6, 147.0, 147.3, 155.8, 156.0<br>HRMS (ESI), $m/z$ (found/calc.): 303.12164/303.12163 ($C_{16}H_{16}N_4ONa$) |
| *IIh* | $^1$H NMR (600 MHz, $CDCl_3$), $\delta$: 4.63 (d, $J$ = 5.9 Hz, 2H, $CH_2$), 4.74 (d, $J$ = 5.7 Hz, 2H, $CH_2$), 5.09 (s, 2H, $CH_2$), 5.20–5.35 (m, 4H, $=CH_2$), 6.0 (m, 2H, CH), 7.29–7.36 (m, 3H, CH″), 7.47 (d, $J$ = 7.8 Hz, 2H, CH″), 7.87 (s, 1H, CH′)<br>$^{13}$C NMR (150.9 MHz, $CDCl_3$), $\delta$: 43.9, 44.5, 48.4, 108.1, 117.6, 119.4, 128.0, 128.4, 128.7, 131.9, 133.0, 136.2, 143.8, 145.7, 150.8, 152.1<br>HRMS (ESI), $m/z$ (found/calc.): 345.13228/345.13220 ($C_{18}H_{18}N_4O_2Na$) |
| *IIi* | $^1$H NMR (600 MHz, $CDCl_3$), $\delta$: 4.55 (m, 2H, $CH_2$), 4.70 (m, 2H, $CH_2$), 5.08 (td, $J$ = 1.8 Hz, $J$ = 17.3 Hz, 1H, $=CH_2$), 5.20 (dd, $J$ = 1.1 Hz, $J$ = 10.2 Hz, 1H, $=CH_2$), 5.30 (m, 2H, $=CH_2$), 5.36 (m, 2H, $CH_2$), 7.03 (d, $J$ = 7.2 Hz, 2H, CH″), 7.45 (m, 3H, CH″), 7.46 (s, 1H, CH′)<br>$^{13}$C NMR (150.9 MHz, $CDCl_3$), $\delta$: 44.0, 45.7, 49.8, 116.6, 117.9, 125.3, 129.0, 129.7, 129.8, 132.0, 132.3, 135.3, 138.6, 138.7, 150.7, 156.8<br>IR, $\tilde{\nu}$/cm$^{-1}$: 3089, 3033, 2930, 2854, 1680, 1572, 1543, 1509, 1496, 1454, 1436, 1425, 1348, 1271, 1203, 1185, 1139, 1107, 1077, 1045, 968, 787, 717, 697, 651<br>HRMS (ESI), $m/z$ (found/calc.): 281.13967/281.13974 ($C_{18}H_{18}N_4O_2 - C_2H_2O + H$) |

*a*) Methine protons of purine moiety are identified by prime and those of phenyl moiety by double prime; *b*) 95 % *E*-isomer (determined by $^1$H NMR); *c*) spectral data given for inseparable mixture of *IIe* and *IIf*; *IIe* was determined (by $^1$H NMR) as 80 % *E*-isomer.

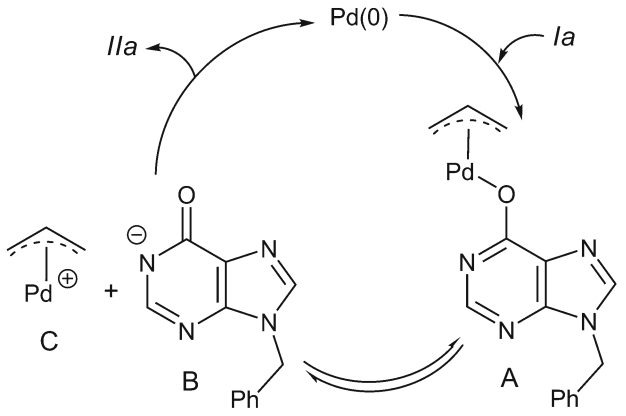


**Fig. 3.** Proposed mechanism for Pd-catalysed rearrangement of allyloxypurines *I*.

Physical and spectral data of 6-allyloxypurines *I* and hypoxanthines *II* are given in Table 3.

The Claisen rearrangement catalysed by zerovalent palladium (Pd(0)) was reported to proceed via $\pi$-allyl intermediate (Schenck & Bosnich, 1985). Our experimental results also accord with this mechanism. We assumed that, in the first step, the $\pi$-allyl palladium complex A was formed through the oxidative addition of Pd(0) (Fig. 3). Complex A is in equilibrium with its dissociated form – $\pi$-allyl palladium cation C and hypoxanthine anion B. Subsequently, anion B acts as nucleophile and adds to the $\pi$-allyl ligand of C giving the final product *IIa* (Fig. 3). The presence of $\pi$-allyl intermediate A was proved by the rearrangement of *Ia* in the presence of $Pd(PPh_3)_4$ and *N*-methylbenzylamine which afforded *N*-allyl-*N*-benzylmethylamine – a product of the nucleophilic addition of *N*-methylbenzylamine to C with 59 % isolated yield. The formation of two isomeric products *IIe* and *IIf* with the same yield and ratio starting either from *Ie* or from *If* (Table 2, entries 5 and 6) also is considered to be the common $\pi$-allyl intermediate. Alternatively, the formation of 9-benzylhypoxanthine during the rearrangement of *Id* in the presence of $Pd(PPh_3)_4$ can be explained by $\beta$-elimination of intermediate $\pi$-allyl complex of type A followed by reductive elimination. This was supported by the detection of the trienes myrcene and (*Z*)-ocimene by $^1$H and $^{13}$C NMR spectroscopy in the crude reaction mixture.

Unlike Pd(0), other metals do not catalyse the rearrangement of *Ia* to *IIa* below 100 °C. This, together with the finding that the rearrangement of *Ie* and *If* does not, unlike *Ia*, proceed at 110 °C, show that these metals operate in accordance with the report of Schenck and Bosnich (1985) by different mechanism.

## Conclusions

Pd(0) catalyses the Claisen rearrangement of 6-, 2-, and 8-allyloxypurines to the corresponding *N*-allyl-6-oxopurines (*N*-allylhypoxanthines). The reaction proceeds via $\pi$-allyl intermediate and can be useful for the synthesis of new purine derivatives with potential biological activity. Other metals such as Cu, Rh or Ru are less active catalysts and most probably operate by different mechanisms.

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