N^1-SUBSTITUTED HYPOXANTHINE DERIVATIVES FROM THE REACTION OF 6-HALOPURINES WITH MICHAEL ACCEPTORS UNDER THE CONDITIONS OF HECK REACTION

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Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday.

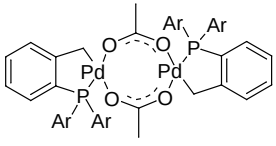
The reaction of 6-iodo-, 9-benzyl-6-chloropurine and 7-benzyl-6-chloropurine with butyl acrylate, acrylonitrile, methyl vinyl ketone or methyl methacrylate under conditions of the Heck reaction in the presence of TlOAc or AgOAc afforded N^1-alkylhypoxanthine derivatives. Formation of these unexpected products can be rationalised as a Tl^+- or Ag^+-assisted substitution of halogen with acetate anion. The 6-acetoxypurine derivative thus formed then eliminates ketene and gives 7-benzyl- or 9-benzylhypoxanthine. Conjugate addition of these compounds onto Michael acceptors furnishes the N^1-substituted hypoxanthine derivatives.
Key words: Purines; Hypoxanthines; Heck reaction; Michael additions; Palladium; Thallium acetate.

The Heck reaction is a well established method for the preparation of functionalised aromatic and heteroaromatic alkenyl derivatives[1]. To the best of our knowledge, this methodology has not been used for synthesis of 6-alkenylpurines. Such reaction would be very useful since some 6-alkenylpurines exhibit biological activity[2] and the C=C double bond can be, in principle, further modified (hydroxylation, hydration, amination, *etc.*), serving as a source of other purine derivatives.

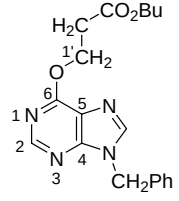
To elaborate this methodology for the synthesis of purine derivatives, we chose the reaction of 9-benzyl-6-iodopurine (**1a**) or 9-benzyl-6-chloropurine (**1b**) with butyl acrylate as a model reaction (Scheme 1). Despite the fact that various catalytic systems, ($[Pd(PPh_3)_4]$, $[Pd(PPh_3)_2Cl_2]$, Herrmann catalyst[3] (**2**), $[Pd_2(dba)_3]\cdot CHCl_3$ in combination with $(2\text{-tolyl})_3P$, $(2\text{-furyl})_3P$, $AsPh_3$ and dppe), bases (Et_3N, $Et(iPr)_2N$, Na_2CO_3, NaOAc) and solvents (acetonitrile, DMF, NMP, toluene) were used, all attempts to obtain the desired butyl 3-(9-benzylpurin-6-yl)propenoate have failed. The unreacted

6-halopurine was always recovered accompanied by 9-benzylpurine (product of dehalogenation) in several cases. This findings are somewhat surprising, since Pd catalysed reactions with alkyl(aryl)zinc or tin reagents[4] as well as Suzuki coupling[5] work well with 6-halopurines.

When the reaction of 9-benzyl-6-iodopurine (**1a**) with butyl acrylate was run in the presence of Hermann catalyst (**2**) and thallium acetate, another product was isolated in a low yield. Its ^{1}H NMR spectrum revealed the presence of butyl group and two triplets with chemical shifts 2.93 and 4.33 ppm, each corresponding to two protons. This clearly shows that the product is a derivative of propanoic but not propenoic acid. HR MS gave the elemental composition $C_{19}H_{22}N_4O_3$. The above data correspond to the hypoxanthine derivatives **3** or **4a**.



2 Ar = 2-tolyl



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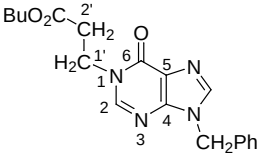
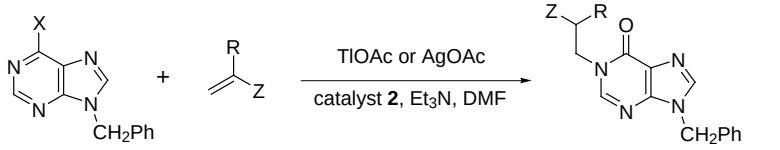


4a

The structure of the product was unambiguously established by HMBC experiment which provides the information on three-bond carbon–proton interactions. The protons at position 1′ interact with carbon atoms in positions 2 and 6, which is possible only for the structure **4a**. Another piece of evidence comes from IR, which shows two carbonyl stretching frequencies at 1 725 and 1 700 cm^{-1} in accordance with the structure **4a**.

When the reaction was run in the presence of 1.5 equivalents of triethylamine, the product **4a** was obtained in 84% yield (Table I, entry 2). The 9-benzyl-6-chloropurine (**1b**) appeared to be somewhat less reactive compared with iodo derivative **1a**, but still giving a high yield of **4a** together with some unreacted **1b** (Table I, entry 3). Other typical Michael acceptors – acrylonitrile, methyl vinyl ketone and methyl methacrylate – reacted similarly to butyl acrylate furnishing *N*^{1}-substituted hypoxanthines **4b**–**4d** (Scheme 1) (Table I, entries 4–6).

Alkenes-like methyl but-2-enoate, methyl cinnamate, 4-methylbut-3-en-2-one, styrene and vinyl acetate were unreactive. Similarly to **1a** and **1b** 7-benzyl-6-chloropurine (**5**) furnished the corresponding hypoxanthine derivative **6** in the reaction (Scheme 2) with butyl acrylate (Table I, entry 7). The structure of compound **6** was also confirmed by HMBC. Interestingly,

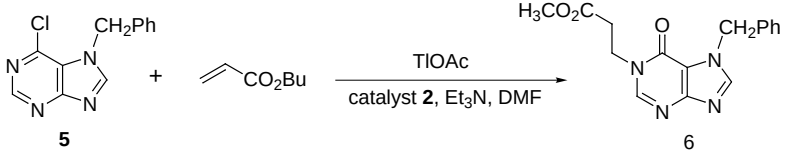


1a, X = I
1b, X = Cl

4a, R = H, Z = CO_2Bu
4b, R = H, Z = CN
4c, R = H, Z = $COCH_3$
4d, R = CH_3, Z = CO_2CH_3

SCHEME 1

whereas silver acetate gave the same results as thallium acetate, other silver salts – benzoate, trifluoroacetate and trifluoromethane sulfonate were ineffective.



5 6

SCHEME 2

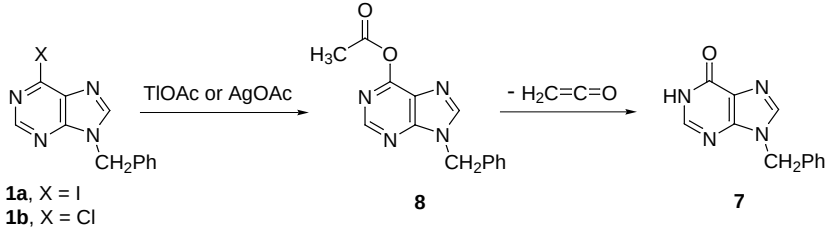
The formation of hypoxanthine derivatives **4a**–**4d** and **6** can be rationalised as a Michael addition of 9-benzylhypoxanthine (**7**) to activated sterically nonhindered alkenes. 9-Benzylhypoxanthine (**7**) was really isolated from the reaction which was run without butyl acrylate under other-

TABLE I
Reaction of 6-halopurines with Michael acceptors under the conditions of Heck reaction[a]

Entry	Halopurine	Michael acceptor	Product (Yield, %)	Entry	Halopurine	Michael acceptor	Product (Yield, %)
1	**1a**	Butyl acrylate[b]	**4a** (20)	5	**1a**	Methyl vinyl ketone	**4c** (72)
2	**1a**	Butyl acrylate	**4a** (84)	6	**1a**	Methyl methacrylate	**4d** (51)
3	**1b**	Butyl acrylate	**4a** (74)[c]	7	**5**	Butyl acrylate	**6** (45)
4	**1a**	Acrylonitrile	**4b** (90)	8	**1a**	Butyl acrylate[d]	**4a** (15)

[a] Reaction conditions: Halopurine 1 equivalent, TlOAc 1.35 equivalent, Et_3N 1.5 equivalent, Michael acceptor 6 equivalents, catalyst **2** 0.06 equivalent, DMF, 80 °C, 20 h; [b] without Et_3N; [c] 20% of **1b** recovered; [d] without Pd catalyst.

wise identical conditions. To explain formation of **7**, we assume Tl^+- or Ag^+-assisted displacement of the halogen in position 6 of purine with acetate anion and formation of 6-acetoxy-9-benzylpurine (**8**), which under the reaction conditions eliminates ketene furnishing 9-benzylhypoxanthine (**7**) (Scheme 3). It appeared, that **7** was also formed in the reaction of 9-benzyl-6-iodoropurine (**1a**) with TlOAc itself (23%), with TlOAc in the presence of Et_3N (45%) and also with TlOAc and catalyst **2** without Et_3N (59%). These reactions were run in DMF at 80 °C for 20 h. The results show, that **7** can be formed directly by the reaction of **1a** with TlOAc and that the reaction is facilitates by Et_3N or by Pd catalyst **2** in absence of triethylamine. The role of triethylamine can be explained by formation of reactive quartery triethyl ammonium salt from triethylamine and **1a** in presence of TlOAc and its subsequent reaction with acetate anion. Triethylamine can also facilitate elimination of ketene. The palladium catalyst **2** may assist in the formation of acetate **8** *via* oxidative addition of palladium followed by displacement of chloride ligand with acetate anion and reductive elimination. Elimination of ketene can proceed intramolecularly in the absence of triethylamine or intermolecularly in its presence. This idea is supported by the well-known high electron deficiency of the purine ring system[6] and the fact that of all the silver salts used, only silver acetate, which can eliminate ketene, furnishes products **4a**–**4d** and **6**.



1a, X = I
1b, X = Cl

8

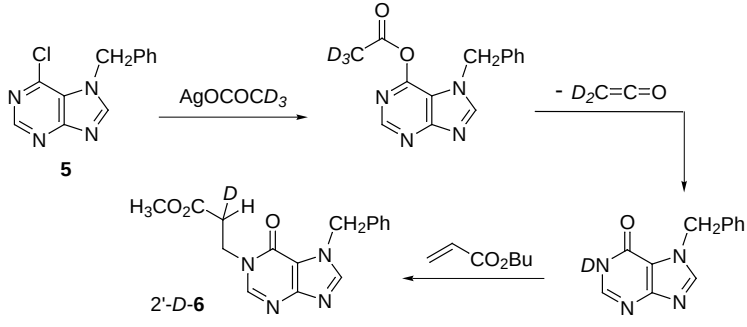
7

SCHEME 3

If the above mechanism really operates, one of the hydrogen atoms in position 2′ of the product should come from acetate. Therefore the reaction of 7-benzyl-6-chloropurine (**5**) with butyl acrylate was repeated in the presence of deuterated silver acetate. Really, 2′-monodeuterated **6** was obtained as evident from its ^1H NMR spectrum (Scheme 4). Another indirect evidence of ketene formation comes from the experiment, in which the volatiles were after reaction distilled under high vacuum directly from the reaction mixture into a dry ice-cooled solution of aniline in toluene. As expected, *N*-acetanilide was isolated from this solution in 32% yield. How-

ever, attempts at a direct proof of ketene in the reaction mixture by GC MS have failed. The last step in the reaction sequence outlined in Scheme 3 – conjugate addition of **7** – was verified by the reaction of independently prepared 9-benzylhypoxanthine (**7**) with butylacrylate. Expected hypoxanthine derivative **4a** was formed in quantitative yield in this reaction no matter what reaction conditions were used (Et_3N, Pd catalyst **2**, Et_3N and Pd catalyst **2** and even without any other additives). Finally, the above mechanism does not require the presence of Pd catalyst. It appeared that the reaction without Pd catalyst really occurs, but slower and with a lower yield (Table I, entry 8). The last finding is in agreement with the above observation that Pd catalyst **2** accelerates formation of **7**.

Whatever the real mechanism of this reaction is, it seems that the Heck reaction is not a useful methodology for the preparation of 6-alkenylpurines. However, the reaction of hypoxanthine derivatives with Michael acceptors might be an efficient route to the compounds of the type **4** and **6**, which are to the best of our knowledge unknown. From 1,9- and 1,7-disubstituted hypoxanthine derivatives only 1,9-dimethylhypoxanthine and 1,7-dimethylhypoxanthine prepared by alkylation of 9-methylhypoxanthine[7] and 7-methylhypoxanthine[8], respectively, were mentioned in literature.



SCHEME 4

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. IR spectra (wavenumbers in cm^{-1}) were recorded on Nicolet 750FT-IR spectrometer. NMR spectra were measured on either a Varian Gemini 300 (^1H, 300.07 MHz; ^{13}C, 75.46 MHz) or a Bruker DRX 500 Avance (^1H, 500.13 MHz; ^{13}C, 125.77 MHz) spectrometers at 298 K. Chemical shifts are given in ppm (δ-scale) and coupling constants (*J*) in Hz. Unambiguous assignment of the NMR signals is based on $^{13}C\{^1H\}$, ^{13}C APT, COSY and ^{13}C HMBC spectra. Mass spectra (FAB) were recorded on ZAB-SEQ (VG Analytical). Elemental analyses were performed by the Analytical De-

partment of Prague Institute of Chemical Technology. All reactions were performed under a dry argon atmosphere. 9-Benzyl-6-chloropurine[4b] (**1b**), 7-benzyl-6-chloropurine[4b] (**5**), 9-benzyl-6-iodopurine[4b] (**1a**) and Herrmann catalyst[3] **2** were by the reported procedures. The light petroleum used refers to the fraction boiling at 40–60 °C. DMF was distilled from P_2O_5 and stored over molecular sieves. Other chemicals were obtained from Aldrich.

Synthesis of Hypoxanthine Derivatives **4a**–**4d** and **6**. General Method

A mixture of 9-benzyl-6-iodopurine (0.168 g, 0.5 mmol), thallium acetate (0.178 g, 0.675 mmol), triethylamine (0.1 ml, 0.75 mmol), Michael acceptor (3 mmol) and Herrmann catalyst (0.016 g, 0.03 mmol) was heated in DMF (3 ml) under argon atmosphere to 80 °C for 20 h. The reaction mixture was then cooled, filtered through Celite, which was washed with a small amount of DMF. The filtrate was then evaporated in vacuum and the residue purified by chromatography on silica (light petroleum–acetone 7 : 3).

9-Benzyl-1-[2-(butoxycarbonyl)ethyl]hypoxanthine (**4a**). The chromatography afforded 0.148 g (83.6%) of the product. Analytical sample was obtained by crystallisation from ether. M.p. 86–87 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): 0.91 t, 3 H, *J* = 7.4 (CH_3); 1.33 m, 2 H (CH_2CH_3); 1.58 m, 2 H ($CH_2CH_2CH_3$); 2.93 t, 2 H, *J* = 6.0 ($NCH_2CH_2CO_2Bu$); 4.08 t, 2 H, *J* = 6.7 ($OCH_2CH_2CH_2CH_3$); 4.33 t, 2 H, *J* = 6.0 ($NCH_2CH_2CO_2Bu$); 5.33 s, 2 H (CH_2Ph); 7.29 m, 2 H (Ph); 7.31–7.40 m, 3 H (Ph); 7.75 s, 1 H (8-PuH); 8.21 s, 1 H (2-PuH). ^{13}C APT NMR (127.77 MHz, $CDCl_3$) CH, CH_3: 14.3 (CH_3), 128.4 (Ph), 129.2 (Ph), 129.8 (Ph), 140.5 (8-Pu), 148.8 (2-Pu); C, CH_2: 19.7 (CH_2), 31.2 (CH_2), 33.8 (CH_2), 43.9 (CH_2), 48.2 (CH_2), 65.6 (CH_2), 125.0 (5-Pu), 135.9 (Ph), 148.6 (4-Pu), 157.3 (6-PuH), 172.2 (C=O). IR ($CHCl_3$): 3 015 m, 2 964 m, 1 725 s, 1 700 s, 1 577 m, 1 548 m, 1 512 m. For $C_{19}H_{22}N_4O_3$ (354.4) calculated: 64.39% C, 6.26% H, 15.81% N; found: 64.34% C, 6.03% H, 15.60% N.

The same reaction starting from 9-benzyl-6-chloropurine (**1b**) afforded **4a** in 74% yield together with 20% of unreacted **1b**.

9-Benzyl-1-(2-cyanoethyl)hypoxanthine (**4b**). The chromatography furnished 0.120 g (90%) of the product. Crystallisation from toluene gave 0.081 g of analytically pure **4b** with m.p. 158–160 °C. ^{1}H NMR (300.07 MHz, $CDCl_3$): 2.98 t, 2 H, *J* = 6.0 (CH_2); 4.32 t, 2 H, *J* = 6.0 (CH_2); 5.34 s, 2 H (CH_2Ph); 7.25–7.40 m, 5 H (Ph); 7.82 s, 1 H (8-PuH); 8.11 s, 1 H (2-PuH). IR ($CHCl_3$): 3 014 w, 1 709 s, 1 576 m, 1 546 m, 1 523 m, 1 359 m. FAB MS, *m/z*: 280.5 $(M + 1)^+$. For $C_{15}H_{13}N_5O$ (279.3) calculated: 64.51% C, 4.69% H, 25.07% N; found: 65.02% C, 5.23% H, 24.99% N.

9-Benzyl-1-(3-oxobutyl)hypoxanthine (**4c**). The product was obtained as an oil 0.106 g (71.6%). ^{1}H NMR (300.07 MHz, $CDCl_3$): 2.13 s, 3 H (CH_3); 3.07 t, 2 H, *J* = 5.8 (CH_2); 4.26 t, 2 H, *J* = 5.8 (CH_2); 5.30 s, 2 H (CH_2Ph); 7.24–7.40 m, 5 H (Ph); 7.74 s, 1 H (8-PuH); 8.25 s, 1 H (2-PuH). IR ($CHCl_3$): 3 012 m, 1 717 s, 1 697 s, 1 578 m, 1 548 m, 1 512 m. FAB HR MS: calculated for $C_{16}H_{17}N_4O_2$ (M + 1) 297.1351; found 297.1336.

9-Benzyl-1-[2-(methoxycarbonyl]propyl]hypoxanthine (**4d**). The chromatography afforded 0.022 g (24%) of oily product together with 0.086 g (51%) of starting 9-benzyl-6-iodopurine. ^{1}H NMR (300.03 MHz, $CDCl_3$): 1.28 d, 3 H, *J* = 7.2 ($CHCH_3$); 3.23 m, 1 H ($CHCO_2CH_3$); 3.64 s, 3 H (CO_2CH_3); 4.04 dd, 1 H, *J* = 9.3, 13.2 (CH_2CH); 4.25 dd, 1 H, *J* = 4.4, 13.2 (CH_2CH); 5.30 s, 2 H (CH_2Ph); 7.24–7.40 m, 5 H (Ph); 7.72 s, 1 H (8-PuH); 8.08 s, 1 H (2-PuH). IR ($CHCl_3$): 3 017 m, 2 928 m, 2 195 m, 1 729 s, 1 703 s, 1 563 m, 1 511 m. FAB HR MS: calculated for $C_{17}H_{19}N_4O_3$ $(M + 1)^+$ 327.1457; found 327.1471.

7-Benzyl-1-[2-(butoxycarbonyl]ethyl]hypoxanthine (**6**). Trapping of Ketene

The reaction of 7-benzyl-6-chloropurine (**5**) (0.743 g, 3.04 mmol), butyl acrylate (2.7 ml, 18.8 mmol), thallium acetate (1.067 g, 4.05 mmol), triethylamine (0.63 ml, 4.5 mmol) and catalyst **2** (0.121 g, 0.13 mmol) in DMF (5 ml) was run as above for 31 h. Approximately 3 ml of the solvent were then distilled in vacuum directly to a solution of aniline (0.3 ml, 3.3 mmol) in dry toluene (5 ml) cooled to –78 °C and left standing at room temperature overnight. Evaporation of toluene and chromatography on silica afforded 0.133 g of acetanilide (32%) identical with an authentic sample. The work-up of the reaction mixture following the general procedure afforded 0.487 g (45.2%) of **6** as a white solid with m.p. 83–85 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): 0.89 t, 3 H, *J* = 7.2 (CH_3); 1.31 m, 2 H (CH_2CH_3); 1.57 m, 2 H ($CH_2CH_2CH_3$); 2.85 t, 2 H, *J* = 6.3 ($NCH_2CH_2CO_2Bu$); 4.07 t, 2 H, *J* = 6.6 ($OCH_2CH_2CH_2CH_3$); 4.28 t, 2 H, *J* = 6.3 ($NCH_2CH_2CO_2Bu$); 5.59 s, 2 H (CH_2Ph); 7.30–7.40 m, 5 H (Ph); 7.87 s, 1 H (8-PuH); 8.16 s, 1 H, (2-PuH). ^{13}C APT NMR (127.77 MHz, $CDCl_3$) CH, CH_3: 13.6 (CH_3), 127.9 (Ph), 128.5 (Ph), 129.0 (Ph), 143.3 (8-Pu), 147.2 (2-Pu); C, CH_2: 19.0 (CH_2CH_3), 30.4 ($CH_2CH_2CH_3$), 33.3 (NCH_2CH_2), 42.8 (NCH_2), 50.6 (CH_2Ph), 64.9 (OCH_2), 115.0 (5-Pu), 135.6 (Ph), 154.3 (6-Pu), 157.1 (4-PuH), 170.9 (C=O). IR ($CHCl_3$): 2 964 m, 1 730 s, 1 688 vs, 1 577 w, 1 500 m, 1 403 m. For $C_{19}H_{22}N_4O_3$ (354.4) calculated: 64.39% C, 6.26% H, 15.81% N; found: 64.43% C, 6.24% H, 15.75% N.

Reaction of 9-Benzyl-6-iodopurine (**1a**) with Thallium Acetate in the Absence of Butyl Acrylate

A mixture of **1a** (0.084 g, 0.25 mmol), thallium acetate (0.072 g, 0.27 mmol), triethylamine (0.05 ml, 0.4 mmol) and catalyst **2** (0.008 g, 0.015 mmol) was heated in DMF (1.5 ml) under argon atmosphere to 80 °C for 20 h. The reaction mixture was then cooled, diluted with dichloromethane and filtered through Celite. The filtrate was then evaporated in vacuum and the residue was purified by HPLC chromatography (Lichrosfer 100 RP-18, methanol–water) affording 0.031 g (55%) of 9-benzylhypoxanthine (**7**). M.p. 290–300 °C (ref.[9] 295–298 °C). ^{1}H NMR (300.07 MHz, DMSO-d_6): 5.37 s, 2 H (CH_2Ph); 7.28–7.34 m, 5 H (Ph); 8.04 s, 1 H (PuH); 8.20 s, 1 H (PuH); identical with that in ref.[10]. FAB MS, *m/z*: 227.5 $(M + 1)^+$.

Reaction of 9-Benzyl-6-iodopurine (**1a**) with Butyl Acrylate in the Presence of Silver Acetate-d_3

The same procedure as above, starting from 9-benzyl-6-iodopurine (0.084 g, 0.25 mmol), catalyst **2** (0.008 g, 0.015 mmol), butyl acrylate (0.18 ml, 1.25 mmol), triethylamine (0.05 ml, 0.3 mmol) and silver acetate-d_3 (0.046 g, 0.27 mmol) in DMF (0.6 ml), gave upon chromatography 0.046g (51.8%) of the product. ^{1}H NMR (300.07 MHz, $CDCl_3$): 0.88 t, 3 H, *J* = 7.2 (CH_3); 1.20–1.40 m, 2 H (CH_2CH_3); 1.49–1.61 m, 2 H ($CH_2CH_2CH_3$); 2.89 m, 1 H ($CHCO_2Bu$); 4.05 t, 2 H, *J* = 6.8 ($OCH_2CH_2CH_2CH_3$); 4.31 m, 2 H (NCH_2CHCO_2Bu); 5.30 s, 2 H (CH_2Ph); 7.23–7.29 m, 2 H (Ph); 7.31–7.39 m, 3 H (Ph); 7.73 s, 1 H (8-PuH); 8.19 s, 1 H (2-PuH).

9-Benzylhypoxanthine (**7**)

This compound was prepared as described for the preparation of 9-benzylguanine[11], by reflux of 9-benzyl-6-chloropurine with 1 equivalent of DABCO in water and acidification in 73% yield. M.p. 286–288 °C (ref.[9] 295–298 °C).

Reaction of 9-Benzylhypoxanthine (**7**) with Butyl Acrylate

A mixture of 9-benzylhypoxanthine (**7**) (0.030 g, 0.133 mmol) and butyl acrylate (0.12 ml, 0.829 mmol) in DMF (2 ml) was heated under argon atmosphere to 80 °C for 20 h. The reaction mixture was then cooled, DMF was evaporated in vacuum and the residue was purified by chromatography on silica (ethyl acetate–methanol 8 : 1) giving 0.047 g (100%) of **4a** as the only product. Similar results were obtained when the reaction was run in the presence of triethylamine, palladim catalyst **2** or the mixture of triethylamine and **2**.

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