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Regioselective Addition of Grignard Reagents to a 2-Oxopurinium Salt

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Abstract: Treatment of 6-ethoxy-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2*H*-purin-2-one with trimethylchlorosilane gave a stable tribenzylated 2-oxopurinium salt, which selectively added Grignard reagents in the 6-position. The structure of the adducts were established from long range HETCOR NMR experiments.

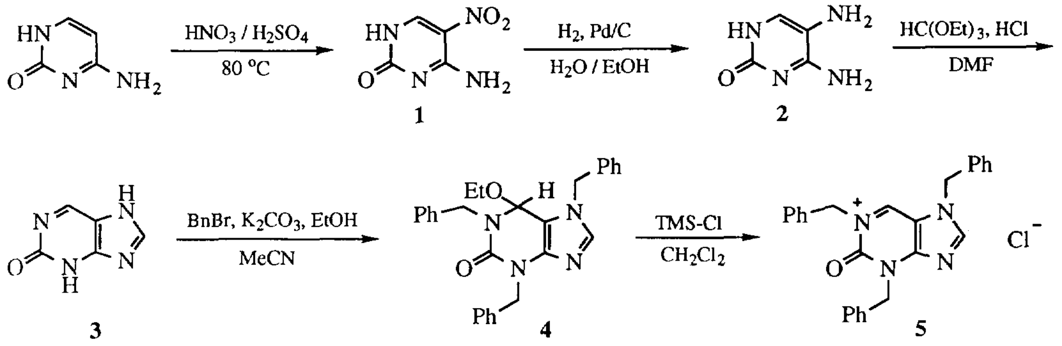
Carbon - carbon bond formation in π-electron deficient heteroarenes can be achieved by addition of an organometallic compound followed by rearomatization of the heterocyclic adduct if desired. The regioselectivity in the additions can frequently be controlled by selecting the right class of organometallic reagent.[1,2] This methodology has only to a limited extent been utilized for the introduction of carbon substituents in purines.[3] Addition of phenyllithium to 6-chloro-9-methylpurine, or its 7-methylated isomer, in the presence of tris(dibenzoylmethido)iron(III), followed by nitrobenzene induced oxidation of the adduct, gave the corresponding 8-phenylpurines in modest yields.[3a] Phenylmagnesium bromide, but not alkylmagnesium halides, is reported to add in the 8-position of 2-cyanopurines.[3b]

2-Purinones are highly polarized compounds as shown by the calculated dipole moments of 1,3-dihydro-2*H*-purin-2-one and tautomers.[4] However, reports on adduct formation of 2-purinones are rare, a few addition reactions on the parent 2-purinone are reported with barbituric acid and potassium hydrogen sulfite as nucleophiles.[5] In reactions between 3,7-dimethyl-6-methylthiopurin-2-one and carbanions of active methylene compounds, nucleophilic substitution in the 6-position takes place.[6] In contrast, Grignard reagents are very recently reported to add in the 8-position of the same purine derivative, even when nickel catalysis is employed. When the 6-position is unsubstituted, selective addition across the *N*-1 - *C*-6 double bond is observed.[7] We have found, however, that neither 1,3-dibenzylpurin-2-one nor its 1,7-dibenzylated isomer added nucleophilic reagents, but that tribenzylated hydroxy- alkoxy- and alkylthioadducts were formed when purin-2-one was alkylated with an excess benzyl bromide in the presence of oxygen- or sulfur nucleophiles.[8] Our hypothesis that these adducts were formed via 3,7-dibenzylpurin-2-one, is supported by the report from Iwamura *et al.*[7]

N-Alkylation or acylation of heterocycles which do not readily add nucleophiles, like pyridines[1c,1h,1i,2a,2b] and imidazo[4,5-c]pyridine,[2c] converts these compounds into heterocyclic cations, highly activated for attack by organometallic derivatives. Even though stable *N*-quaternary purinium compounds are known,[9] the electrophilicity of these species has, to our knowledge, not been utilized for *C* - *C* bond formations. In connection with our ongoing project directed towards development of methodology for *C*-alkylation and arylation of purines,[10] we herein report on the formation of a stable 2-oxopurinium salt, which undergoes regioselective addition of organometallic reagents.

RESULTS AND DISCUSSION

2-Purinone was first synthesized by Tafel and Ach in three steps from guanine,[11] but we chose to make this compound from cytosine as reported by Holy.[12] However, several steps in this synthesis appeared to be difficult to reproduce and modifications had to be made (Scheme 1).



Scheme 1

Nitration of cytosine with anhydrous nitric acid[12] gave only 5 % of the desired 5-nitrocytosine **1**, but heating cytosine at 80 °C with a mixture of anhydrous nitric acid and conc. sulfuric acid allowed isolation of the nitration product **1** in 92 % yield. Catalytic hydrogenation of **1** to 5-aminocytosine **2** at atmospheric pressure in water as described by Holy,[12] gave again disappointing results, and we found that an H_2 pressure of ca. 50 psi. was required. The use of ethanol as co-solvent was also beneficial to the reaction. With these modifications, 5-aminopyrimidine **2** could be prepared in 85 % yield. Final ring closure of the diaminopyrimidine with triethyl orthoformate to give the 2-purinone **3** was carried out as previously described,[12] giving 82 % of the purine **3**, a higher yield than reported by Holy.[12] Care must be taken, however, because of the instability of the purine **3** in aqueous solution.[13] Alkylation of **3** with 3 equiv. benzyl bromide in the presence of ethanol gave 6-ethoxy-1,3,7-tribenzylpurin-2-one **4**[8] in 61 % yield together with 28 % of 1,3-dibenzylpurin-2-one[8] and a small amount of other benzylated isomers. When the same reaction was performed using benzyl chloride as the alkylating agent, only 4 % of the tribenzylated adduct could be isolated.

Trimethylsilyl halides are known to promote cleavage of ethers, epoxides, acetals and esters.[14] The ethoxy group in the purine adduct **4** could be removed under extremely mild condition, simply by adding 1.2 equiv. of trimethylchlorosilane to a dichloromethane solution of **4**. The purinium chloride **5** was formed together with ethoxy(trimethyl)silane, as judged by ^{1}H NMR of the reaction mixture. In Scheme 1, the compound **5** is arbitrarily represented by one of many possible resonance forms. The purinium salt **5** was easily separated from the lipophilic silane co-product by addition of ether which precipitated the former. Crude anhydrous purinium chloride **5** could be stored for a prolonged time under N_2 atmosphere. However, the compound appears to be relatively hygroscopic; when the crude salt was crystallized from dichloromethane / hexane, purinium chloride monohydrate was formed. Cationic purinium species

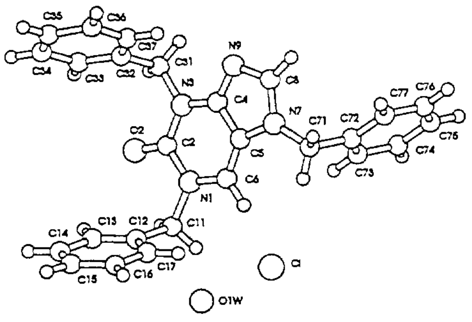
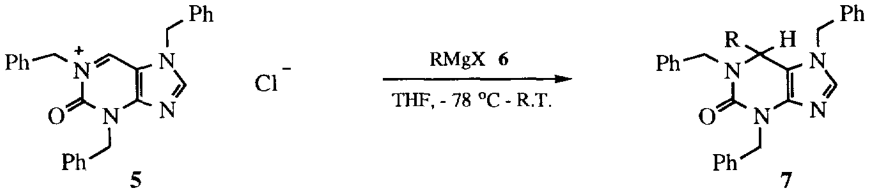


Fig. 1. Molecular conformation and atom labeling scheme of compound **5** as monohydrate.

like 5, could also be generated when the ethoxypurine **4** was treated with protic acids, like TFA or H_2SO_4.

The characterization of the compound **5** as a cationic purinium salt was initially based on ^{1}H NMR spectroscopy. Whereas the benzylic CH_2 protons in the ethoxy adduct **4** gave rise to AB patterns,[8] the CH_2 protons in **5** resonated as singlets, indicating that a stereogenic center was no longer present. Furthermore, low field shifts of the resonances belonging to *H*-6 and *H*-8 were observed. Similar low field shifts are observed in ^{1}H NMR spectra of pyridinium cations.[2a] The structure of the compound **5** was also established by X-ray crystallography (Fig. 1).

Addition of Grignard reagents **6** to the purinium compound **5** allowed introduction of alkynyl-, alkenyl-, aryl- and alkyl substituents (Scheme 2, Table 1).



Scheme 2

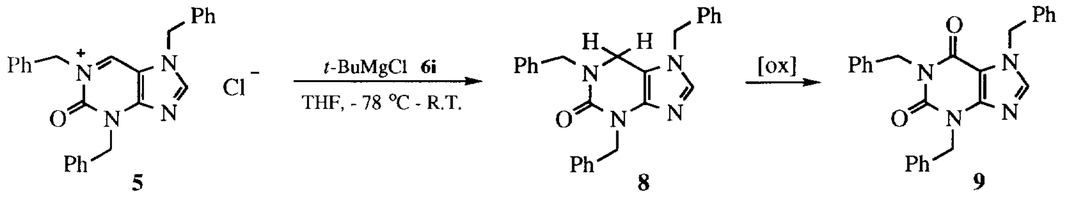
Table 1. Addition of Grignard Reagents **6** to the Purinium Salt **5**.

RMgX **6**		Product **7**	Yield (%)
PhC≡CMgBr	**6a**	**7a**	71
CH_2=CHMgBr	**6b**	**7b**	69
PhMgBr	**6c**	**7c**	51
CH_3MgBr	**6d**	**7d**	88
CH_3CH_2MgBr	**6e**	**7e**	75
n-C_4H_9MgCl	**6f**	**7f**	68
n-$C_{10}H_{21}MgBr$	**6g**	**7g**	76
$(CH_3)_2CHMgCl$	**6h**	**7h**	46

The organometallic reagents could, in principle, attack in the purine 4-, 6- or 8-position. However, in all cases examined, only one isomer was formed. The X-ray structure of **5** indicate that the 6-position is more hindered than the 8-position in crystalline **5**, but ^{1}H NMR spectroscopy revealed that the addition had taken place in the 6-position exclusively, to give the adducts **7a** - **h** (*vide infra*), generally in high yields. The somewhat more moderate yields obtained adding phenylmagnesium bromide **6c** and isopropylmagnesium chloride **6h** might be attributed to the larger sterical requirements of these reagents. These results show that the cationic purinium compound **5** is highly activated for nucleophilic attack compared to the neutral 3,7-

dimethylpurin-2-one. Addition of Grignard reagents to the latter purine requires a large excess of organometallic reagent and elevated temperature.[7] Attempts to add organolitium reagents, phenyllithium or *n*-butyllithium, to the purinium salt **5** at - 78 °C, resulted only in decomposition of the starting material **5** and no addition products could be detected.

When the purinium salt **5** was reacted with *tert*-butylmagnesium chloride **6i**, no *tert*-butyl adduct was formed. Instead, 1,3,6,7-tetrahydro-1,3,7-tribenzylpurin-2-one **8** could be isolated in 77 % yield (Scheme 3). The formation of the product **8** can be explained by β-elimination from the organomagnesium reagent followed by hydride addition to the purinium derivative **5**. β-Elimination from sterically hindered Grignard reagents is not uncommon,[15] and it is noteworthy that no hydride addition at all was observed when the secondary Grignard reagent isopropylmagnesium chloride **7h** was added to the purine **5**.

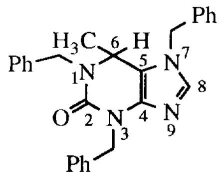


Scheme 3

When crystals or solutions of the purine **8** were exposed to air, oxidation to tribenzylxanthine **9** could be observed after a short time. After 60 days the conversion of the purine **8** to the xanthine **9** was ca. 68 % as judged by ^{1}H NMR, and **9** was isolated in 45 % yield. We were somewhat surprised by the low stability of the adduct **8**. Even though the corresponding 1,3,6,7-tetrahydro-1,3,7-trimethylpurin-2-one has been known for a long time,[16] no reports on oxidation of this compound to 1,3,7-trimethylxanthine (caffeine) exists in the literature. The purine adducts **7** were relatively stable under inert atmosphere, but slow decomposition in solution was generally observed.

The site of *N*-alkylation in purines has been determined by long range HETCOR[17] or long range selective INEPT NMR experiments,[8,18] in this study, we employed long range ^{1}H^{13}C HETCOR, to reveal the substitution pattern of the adducts **7**. A detailed description of the structure elucidation of the methyl adduct **7d** follows (Table 2).

Table 2. Selected Correlations from the Long Range HETCOR Spectrum of the Adduct **7d**.



7d

	C-2	C-4	C-5	C-6	C-8
CH_2(N1)	X			X	
CH_2(N3)	X	X			
CH_2(N7)			X		X
CH_3			X	X	
H-6	X	X	X	X	
H-8		X	X		X

The ^1H and ^{13}C resonances were partly assigned by DEPT and HETCOR experiments. A long range HETCOR spectrum optimized for 10 Hz couplings, revealed correlations between protons and carbons up to three bonds apart. Correlations between four of the six CH_2 protons and the lowest field ^{13}C resonance (153.5 ppm) were observed. This ^{13}C resonance was assigned to the *C*-2 in the purine skeleton and the CH_2 protons to the benzyl groups in the 1- and 3-position. Two of these benzylic CH_2 protons correlated with the quartenary carbon resonating at 138.8 ppm, showing these protons to be situated in the *N*-3 substituent and the carbon to be *C*-4. The CH_2 protons from the *N*-1 substituent correlated with the tertiary carbon resonating at 48.5 ppm. HETCOR had shown the high field ^{13}C resonance to correlate with the quartet in the ^1H spectrum (4.17 ppm), telling us that the methyl substituent was situated at this carbon. The correlation between The *N*-1 CH_2 protons and the high field carbon proved that addition had taken place in the purine 6-position. The resonances belonging to the two last purine ring carbons (*C*-5 and *C*-8) were assigned on the basis of long distance correlations with the CH_2 protons in the *N*-7 benzyl group. Furthermore, the structure of the adduct **7d** was confirmed by correlations between *H*-6 and *C*-2, *C*-4 and *C*-5, and between the CH_3 protons and *C*-6 and *C*-5. Selected correlations are shown in Table 2. The structure of the other adducts were determined in an analogous fashion.

The regioselective addition of Grignard reagents to the stable purinium salt **5** is a novel method for carbon-carbon bond formation in the purine 6-position, complementary to transition metal catalyzed coupling of halopurines with organometallic reagents.[10] The reactivity and regioselectivity of other organometallic reagents in these addition reactions are currently under investigation. It is envisaged that 6-substituted aromatic purines can be prepared, if addition of organometallic reagents are performed on purinium salts with easily removable *N*-substituents followed by cleavage of the *N*-protecting groups and subsequent rearomatization of the adducts.

EXPERIMENTAL

General information. The ^1H NMR spectra were recorded at 300 MHz with a Varian XL-300 (manual) or at 200 MHz with a Varian Gemini 200 instrument. The ^{13}C NMR spectra were recorded at 75 or 50 MHz using the above mentioned instruments. $^1H^{13}C$ HETCOR and $^1H^{13}C$ long range HETCOR experiments optimized for 10 Hz coupling constants were performed on the above mentioned spectrometers. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Mass spectra were recorded at 70 eV ionizing voltage and are presented as *m/z* (% rel. int.). Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points are uncorrected. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck no. 9385). THF was distilled from sodium / benzophenone, DMF from barium oxide and dichloromethane and trimethylchlorosilane from calcium hydride. The Grignard reagents were purchased in Sure/Seal™ bottles from Aldrich Chemical Company, Steinheim, Germany. All other reagents were commercially available and used as received.

*X-ray analysis of 2,7-dihydro-1,3,7-tribenzyl-2-oxo-1*H*-purinium chloride monohydrate 5.* $[C_{26}H_{23}N_4O]^+Cl^- \cdot H_2O$, Mw 460.97, crystals obtained from a mixture of CH_2Cl_2 and hexane, crystal size 0.19x0.36x0.48 mm, monoclinic, space group $P2_1$ / a, Z=4, a=17.3820(23), b=8.7039(15), c=17.4986(18) Å, β=116.956(11)°, V=2359.6(9) $Å^3$, d_c=1.297 g cm^{-3}, λ(Cu Kα)=1.5418 Å, μ=1.68 mm^{-1}.

Intensity data ($1<\theta<70°$) were measured on an Enraf-Nonius CAD-4 diffractometer using the θ / 2θ scan mode. A total of 4463 unique reflections were recorded, and of these 3258 with $I>2.5\ \sigma(I)$ were considered observed. Cell parameters were obtained from the angular setting of 25 reflections ($30<\theta<48°$). The structure was solved by direct methods using the NRCVAX[19] program and refined by the full-matrix least-squares method using anisotropic displacement factors for the non-hydrogen atoms. The hydrogen atoms were included at the theoretical positions (C-H 1.00 Å) and assigned an isotropic displacement factor equal to the U_{eq} value of the parent atom. The positions of the water hydrogens were not determined. The hydrogen atom parameters were not refined. Convergence was reached at R=0.110 and R_w=0.108 with w=1 / σ^2(Fo) from counting statistics. A final difference map showed no peaks greater than 0.9 e Å^{-3}. The molecular conformation and atom labeling scheme are shown in Fig. 1. The structure parameters have been deposited at the Cambridge Crystallographic Data Center, U.K.

5-Nitrocytosine (1).[12] Cytosine (40.36 g, 0.363 mol) was added over 45 min. to a stirring mixture of anhydrous nitric acid (250 ml) and conc. sulfuric acid (50 ml). The resulting mixture was heated at 80 °C for 18 h, poured onto ice (2 kg) and neutralized with sat. aq. NaOH. The solid was filtered off, dissolved in hot water (2 l) and the pH adjusted to 12 with NaOH. The solution was neutralized with conc. acetic acid and cooled in a refrigerator over night, before the solid formed was filtered off, washed with ice-cold water, ice-cold abs. EtOH and ice-cold diethyl ether, and dried *in vacuo*; yield 52.24 g (92 %), white solid; M.p. > 200 °C (dec.). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 8.13 (br s, NH_2), 8.84 (s, H-6). MS (EI): 156 (100, M^+).

5-Aminocytosine (2).[12] 5-Nitrocytosine (20.78 g, 0.133 mol) in water (140 ml) and ethanol (70 ml) was reduced with H_2-gas (50 psi.) in a Parr apparatus in the presence of palladium on charcoal (1.503 g) until no more H_2 was absorbed. The mixture was filtered, the solid extracted with hot water (4 x 200 ml) and the combined filtrates evaporated *in vacuo*. The product was crystallized from water; yield 14.24 g (85 %), yellow crystals; M.p. > 200 °C (dec.). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.79 (br s, NH_2) 6.75 (s, H-6). MS (EI): 126 (100, M^+).

1,3-Dihydro-2H-purin-2-one (3).[12] Triethyl orthoformate (50 ml) and 5-aminocytosine (6.882 g, 54.6 mmol) was added to a solution of HCl (4.42 g) in dry DMF (70 ml) and the resulting mixture was stirred at ambient temperature under N_2-atmosphere for 4 days, made alkaline with triethylamine and concentrated *in vacuo*. The residue was crystallized from water; yield 6.091 g (82 %); M.p. > 200 °C (dec.). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 8.63 (s, 1H), 8.92 (s, 1H). MS (EI): 136 (100, M^+).

6-Ethoxy-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2H-purin-2-one (4).[8] Benzyl bromide (1.08 ml, 9.09 mmol) was added to a stirring suspension of 1,3-dihydro-2*H*-purin-2-one (408 mg, 3.00 mmol) and potassium carbonate (840 mg, 6.08 mmol) in acetonitrile (10 ml) at ambient temperature under N_2-atmosphere and the resulting mixture was stirred for 2 h, before ethanol (2 ml) was added. After stirring for an additional 15 h, the mixture was evaporated *in vacuo* and the product isolated by flash chromatography on silica gel eluting with $CHCl_3$ / MeCN (10:1) and gradually increasing the amount of MeCN to $CHCl_3$ / MeCN (1:1); yield 827 mg (61 %) colourless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.85 (t, *J* 7.0 Hz, 3H, Me), 2.74 (m, 1H, CH_2O), 2.98 (m, 1H, CH_2O), 4.19 (d, *J* 15.0 Hz, 1H, N(1)CH_2), 4.89 (d, *J* 14.9 Hz, 1H, N(7)CH_2), 4.92 (d, *J* 14.9 Hz, 1H, N(7)CH_2), 5.07 (d, *J* 9.5 Hz, 1H, N(3)CH_2), 5.08 (d, *J* 9.5 Hz, 1H, N(3)CH_2), 5.18 (d, *J* 15.0 Hz, 1H, N(1)CH_2), 5.71 (s, 1H, H-6), 6.9-7.4 (m, 16H, Ph and H-8). MS (EI): 452 (2, M^+), 91 (100).

2,7-Dihydro-1,3,7-tribenzyl-2-oxo-1H-purinium chloride (5). Trimethylchlorosilane (0.198 ml, 1.56 mmol) was added to a stirring solution of 6-ethoxy-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2*H*-purin-2-one (586 mg, 1.3 mmol) in dry dichloromethane (8 ml). After 1 h, diethyl ether (14 ml) was added and the mixture stirred for a short period before the solid was filtered off and dried *in vacuo*; yield 426 mg (74 %) anhydrous **5** as a yellow solid. Crystallization from CH_2Cl_2 / hexane gave **5** monohydrate as colourless crystals; M.p. 178 - 180 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 5.34, 5.41 and 5.71 (s, 2H, CH_2), 7.0-7.8 (m, 16H), 9.42 (s, 1H), 10.69 (s, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 48.5, 49.6 and 55.7 (CH_2), 116.4 (C-5), 128.1-128.9 (CH in Ph), 134.1, 134.4 and 134.8 (C in Ph), 144.0 (C-6/C-8), 147.5 (C-2/C-4), 155.9 (C-6/C-8), 158.3 (C-2/C-4). MS (EI): 407 (8, M^+), 395 (8), 332 (5), 317 (7), 288 (5), 226 (11), 198 (14), 91 (100); Hrms calcd for $C_{26}H_{23}N_4O$: 407.1872; found 407.1859.

Addition of Grignard reagents (6) to 2,7-dihydro-1,3,7-tribenzyl-2-oxo-1H-purinium chloride (5). A 1 M solution of the desired Grignard reagent in THF (0.45 mmol) was added dropwise over 20 min to a solution of anhydrous 2,7-dihydro-1,3,7-tribenzyl-2-oxo-1*H*-purinium chloride (168 mg, 0.38 mmol) in dry THF (15 ml) at - 78 °C under N_2-atmosphere and the resulting mixture was stirred over night while gradually reaching ambient temperature. Sat. aq. ammonium chloride (20 ml) was added, the phases separated and the aqueous layer extracted with 3 x 20 ml EtOAc. The combined organic extracts were dried ($MgSO_4$), evaporated and the product was isolated by flash chromatography on silica gel.

*6-Phenylethynyl-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2*H*-purin-2-one (7a).* Compound **7a** was prepared from phenylethynylmagnesium bromide **6a** as described above and isolated by flash chromatography eluting with hexane followed by EtOAc/hexane (1:3), EtOAc/hexane (1:2) and EtOAc/hexane (1:1); yield 137 mg (71 %), colourless crystals. M. p. 132-135 °C. ^{1}H NMR (CD_2Cl_2, 200 MHz): δ 4.30 (d, *J* 15.2 Hz, 1H, N(1)CH_2), 5.0-5.1 (m, 4H, N(7)CH_2 and N(3)CH_2), 5.19 (s, 1H, H-6), 5.44 (d, *J* 15.2 Hz, 1H, N(1)CH_2), 7.1-7.5 (m, 21H, Ph and H-8). ^{13}C NMR (CD_2Cl_2, 50 MHz): δ 45.6 (N(3)CH_2), 46.0 (C-6), 49.3 (N(1)CH_2), 49.9 (N(7)CH_2), 84.8 and 86.1 (C≡), 103.2 (C-5), 122.1 (C in Ph), 127.2-132.1 (CH in Ph), 135.0 (C-8), 135.5 and 137.3 (C in Ph), 139.1, (C-4), 139.4 (C in Ph), 152.7 (C-2). MS (EI): 508 (16, *M*+), 507 (17), 481 (4), 422 (20), 407 (12), 331 (6), 288 (9), 226 (8), 198 (10), 104 (12), 91 (100); Hrms calcd for $C_{34}H_{28}N_4O$: 508.2263; found 508.2268.

*6-Ethenyl-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2*H*-purin-2-one (7b).* Compound **7b** was prepared from ethenylmagnesium bromide **6b** as described above and isolated by flash chromatography eluting with hexane followed by EtOAc/hexane (1:3), EtOAc/hexane (1:2) and EtOAc/hexane (1:1); yield 113 mg (69 %), colourless crystals. M.p. 112 - 113 °C ^{1}H NMR (CD_2Cl_2, 200 MHz): δ 3.93 (d, *J* 15.5 Hz, 1H, N(1)CH_2), 4.59 (d, *J* 8.8 Hz, 1H, H-6), 4.82 (d, *J* 15.6 Hz, 1H, N(7)CH_2), 4.99 (d, *J* 15.6 Hz, 1H, N(7)CH_2), 5.0-5.2 (m, 2H, CH_2=), 5.05 (d, *J* 15.3, 1H, N(3)CH_2), 5.10 (d, *J* 15.3, 1H, N(3)CH_2), 5.30 (d, *J* 15.1 Hz, 1H, N(1)CH_2), 5.6-5.8 (m, 1H, CH=), 6.9-7.6 (m, 16H, Ph and H-8). ^{13}C NMR (CD_2Cl_2, 50 MHz): δ 45.5 (N(3)CH_2), 48.2 (N(1)CH_2), 49.5 (N(7)CH_2), 57.3 (C-6), 104.7 (C-5), 117.6 (CH_2=), 126.2-128.3 (CH in Ph), 134.1 (C-8), 134.9 (C in Ph), 135.5 (CH=), 137.0 (C in Ph), 138.2 (C-4), 138.7 (C in Ph), 152.2 (C-2). MS (EI): 434 (34, *M*+), 422 (4), 407 (82), 343 (7), 302 (3), 238 (3), 210 (2), 181 (4), 91 (100), 77 (3), 65 (7); Hrms calcd for $C_{28}H_{26}N_4O$: 434.2107; found 434.2096.

*6-Phenyl-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2*H*-purin-2-one (7c).* Compound **7c** was prepared from phenylmagnesium bromide **6c** as described above and isolated by flash chromatography eluting with hexane followed by EtOAc/hexane (1:3), EtOAc/hexane (1:2) and EtOAc/hexane (1:1); yield 94 mg (51 %), colourless crystals M.p. 172 - 176 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.38 (d, *J* 15.5 Hz, 1H, N(1)CH_2), 4.31 (d, *J* 15.7 Hz, 1H, N(7)CH_2), 4.61 (d, *J* 15.7 Hz, 1H, N(7)CH_2), 4.99 (s, 1H, H-6), 5.11 (d, *J* 15.0 Hz, 1H, N(3)CH_2), 5.20 (d, *J* 15.0 Hz, 1H, N(3)CH_2), 5.31 (d, *J* 15.5 Hz, 1H, N(1)CH_2), 6.6-7.5 (m, 21H, Ph and H-8). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 45.6 (N(3)CH2), 47.8 (N(1)CH2), 49.2 (N(7)CH_2), 57.3 (C-6), 107.4 (C-5), 126.7-129.0 (CH in Ph), 134.5 (C-8), 134.6 and 136.9 (C in Ph), 138.3 (C-4), 138.7 and 139.6 (C in Ph), 152.9 (C-2). MS (EI): 484 (40, *M*+), 422 (6), 407 (85), 393 (12), 352 (6), 315 (1), 288 (5), 260 (3), 226 (2), 198 (6), 91 (100), 65 (6); Hrms calcd for $C_{32}H_{28}N_4O$: 484.2263; found 484.2245.

*6-Methyl-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2*H*-purin-2-one (7d).* Compound **7d** was prepared from methylmagnesium bromide **6d** as described above and isolated by flash chromatography eluting with hexane followed by EtOAc/hexane (1:3), EtOAc/hexane (1:2) and EtOAc/hexane (1:1); yield 141 mg (88 %), yellow crystals. M.p. 129-131 °C. (Found: C, 76.70; H, 6.14. Calc. for $C_{27}H_{26}N_4O$: C, 76.75; H, 6.20 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.09 (d, *J* 5.9 Hz, 3H, Me), 3.90 (d, *J* 15.4 Hz, 1H, N(1)CH_2), 4.17 (q, *J* 6.1 Hz, 1H, H-6), 4.73 (d, *J* 15.8 Hz, 1H, N(7)CH_2), 4.85 (d, *J* 15.8 Hz, 1H, N(7)CH_2), 4.99 (d, *J* 15.2 Hz, 1H, N(3)CH_2), 5.10 (d, *J* 15.2 Hz, 1H, N(3)CH_2), 5.25 (d, *J* 15.4 Hz, 1H, N(1)CH_2), 6.8-7.4 (m, 16H, Ph and H-8). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.9 (Me), 45.1 (N(3)CH_2), 48.5 (C-6), 48.6 (N(1)CH_2), 49.3 (N(7)CH_2), 108.5 (C-5), 126.6-128.9 (CH in Ph), 134.8 (C-8), 134.9, 137.4 and 138.4 (C in Ph), 138.8 (C-4), 153.5 (C-2). MS (EI): 422 (17, M^+), 407 (100), 329 (3), 290 (3), 239 (4), 226 (2), 207 (3), 181 (4), 116 (3), 91 (82), 65 (4).

*6-Ethyl-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2*H*-purin-2-one (7e).* Compound **7e** was prepared from ethylmagnesium bromide **6e** as described above and isolated by flash chromatography eluting with hexane followed by EtOAc/hexane (1:1); yield 124 mg (75 %), colourless crystals. M.p. 133-135 °C. (Found: C, 76.90; H, 6.35. Calc. for $C_{28}H_{28}N_4O$: C, 77.03; H, 6.47 %). ^{1}H NMR (CD_2Cl_2, 200 MHz): δ 0.67 (t, *J* 7.4, Hz, 3H, CH_3), 1.1-1.4 (m, 1H, CH_2), 1.7-2.0 (m, 1H, CH_2), 3.92 (d, *J* 15.5 Hz, 1H, N(1)CH_2), 4.40 (m, 1H, H-6), 4.86 (d, *J* 15.5 Hz, 1H, N(7)CH_2), 5.0 (m, 2H, N(3)CH_2), 5.13 (d, *J* 15.5 Hz, 1H, N(7)CH_2), 5.32 (d, *J* 15.5 Hz, 1H, N(1)CH_2), 6.9-7.4 (m, 16H, Ph and H-8). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 6.5 (CH_3), 25.0 (CH_2), 44.4 (N(7)CH_2), 47.8 (N(1)CH_2), 48.2 (N(3)CH_2), 53.2 (C-6), 105.1 (C-5), 126.5-128.6 (CH in Ph), 135.2 (C-8), 136.6, 138.0 and 139.1 (C in Ph), 139.3 (C-4), 153.5 (C-2). MS (EI): 436 (3, M^+), 407 (100), 315 (2), 290 (2), 225 (2), 181 (2), 91 (61), 65 (4).

*6-*n*-Butyl-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2*H*-purin-2-one (7f).* Compound **7f** was prepared from *n*-butylmagnesium chloride **6f** as described above and isolated by flash chromatography eluting with hexane followed by EtOAc/hexane (1:1); yield 120 mg (68 %), colourless crystals. M.p. 120-121 °C. ^{1}H NMR (CD_2Cl_2, 200 MHz): δ 0.77 (t, *J* 6.6 Hz, 3H, CH_3), 0.9-1.3 (m, 4H, CH_2), 1.7-2.0 (m, 2H, CH_2), 3.98 (d, *J* 15.6 Hz, 1H, N(1)CH_2), 4.4 (m, 1H, H-6), 4.90 (d, *J* 15.8 Hz, 1H, N(3)CH_2), 4.99 (d, *J* 15.8 Hz, 1H, N(3)CH_2), 5.03 (d, *J* 15.0 Hz, 1H, N(7)CH_2), 5.16 (d, *J* 15.0 Hz, 1H, N(7)CH_2), 5.30 (d, *J* 15.6 Hz, 1H, N(1)CH_2), 6.9-7.5 (m, 16H, Ph and H-8). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 14.0 (CH_3), 22.0, 24.5 and 32.2 (CH_2 in *n*-Bu), 44.5 (N(7)CH_2), 48.2 (N(3)CH_2), 48.3 (N(1)CH_2), 53.0 (C-6), 105.8 (C-5), 126.7-128.7 (CH in Ph), 135.3 (C-8), 136.9 and 138.3 (C in Ph), 139.15 (C-4), 139.22 (C in Ph), 153.6 (C-2). MS (EI): 464 (4, M^+), 407 (100), 316 (3), 290 (2), 225 (4), 211 (1), 181 (3), 111 (1), 91 (71), 65 (4); Hrms calcd for $C_{30}H_{32}N_4O$: 464.2576; found 464.2576.

*6-*n*-Decyl-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2*H*-purin-2-one (7g).* Compound **7g** was prepared from *n*-decylmagnesium bromide **6g** as described above and isolated by flash chromatography eluting with hexane followed by EtOAc/hexane (1:3), EtOAc/hexane (1:2) and EtOAc/hexane (1:1); yield 158 mg (76 %), colourless crystals. M.p. 75-76 °C. ^{1}H NMR (CD_2Cl_2, 200 MHz): δ 0.6-1.8 (m, 21H, *n*-decyl), 3.99 (d, *J* 15.7 Hz, 1H, N(1)CH_2), 4.4 (m, 1H, H-6), 4.91 (d, *J* 15.9 Hz, 1H, N(3)CH_2), 4.99 (d, *J* 15.9 Hz, 1H, N(3)CH_2), 5.02 (d, *J* 15.2 Hz, 1H, N(7)CH_2), 5.16 (d, *J* 15.2 Hz, 1H, N(7)CH_2), 5.29 (d, *J* 15.7 Hz, 1H, N(1)CH_2), 7.2-7.8 (m, 16H, Ph and H-8). ^{13}C NMR (CD_2Cl_2, 50 MHz): δ 14.7 (Me), 23.4, 29.9, 30.1, 30.2, 32.6, 33.7 (CH_2 in decyl), 45.4 (N(3)CH_2), 48.9 (N(1)CH_2), 49.8 (N(7)CH_2), 53.7 (C-6), 106.1 (C-5), 126.0-128.3 (CH in Ph), 133.8 (C-8), 135.1, 137.3 and 138.8 (C in Ph), 149.2 (C-4), 153.3 (C-2), 2 CH_2 were hidden. MS (EI): 548 (1, M^+), 407 (100), 316 (2), 290 (2), 225 (2), 181 (3), 129 (3), 91 (78), 79 (1), 65 (4), 55 (2); Hrms calcd for $C_{36}H_{44}N_4O$: 548.3515; found 548.3508.

*6-isopropyl-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2*H*-purin-2-one (7h).* Compound **7h** was prepared from isopropylmagnesium bromide **6h** as described above and isolated by flash chromatography eluting with hexane followed by EtOAc/hexane (1:3), EtOAc/hexane (1:2) and EtOAc/hexane (1:1); yield 79 mg (46 %), colourless crystals. M.p. 142-144 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.79 (d, *J* 6.9 Hz, 3H, Me), 0.87 (d, *J* 6.9 Hz, 3H, Me), 1.9-2.1 (m, 1H, CH), 3.93 (d, *J* 15.6, 1H, N(1)CH_2), 4.18 (d, *J* 3.3 Hz, 1H, H-6), 4.90 (d, *J* 15.5, 1H, N(7)CH_2), 4.99 (d, *J* 15.8, 1H, N(3)CH_2), 5.06 (d, *J* 15.8, 1H, N(3)CH_2), 5.12 (d, *J* 15.5, 1H, N(7)CH_2), 5.32 (d, *J* 15.6, 1H, N(1)CH_2), 6.8-7.4 (m, 16H, Ph and H-8). ^{13}C NMR (CD_2Cl_2, 50 MHz): δ 17.7 and 18.9 (Me), 33.9 (CH), 45.6 (N(3)CH_2), 50.3 (N(1)CH_2), 50.8 (N(7)CH_2), 58.8 (C-6), 105.6 (C-5), 126.0-128.4 (CH in Ph), 134.4 (C-8), 135.2, 137.4 and 138.5 (C in Ph), 140.4 (C-4), 153.8 (C-2). MS (EI): 450 (1, M^+), 407 (100), 316 (1), 290 (2), 225 (2), 181 (3), 91 (87), 65 (5); Hrms calcd for $C_{29}H_{30}N_4O$: 450.2420; found 450.2437.

*1,3,6,7-Tetrahydro-1,3,7-tribenzyl-2*H*-purin-2-one (8).* Compound **8** was prepared from *tert*-butylmagnesium chloride **6i** as described above and isolated by flash chromatography eluting with hexane followed by EtOAc/hexane (1:3), EtOAc/hexane (1:2) and EtOAc/hexane (1:1); yield 119 mg (77 %), colourless crystals. M.p. 132 - 135 °C. ^{1}H NMR (CD_2Cl_2, 200 MHz): δ 4.18 (s, 2H, H-6), 4.57 (s, 2H, N(1)CH_2), 4.93 (s, 2H, N(7)CH_2), 5.04 (s, 2H, N(3)CH_2), 7.0-7.5 (m, 16H, Ph and H-8). ^{13}C NMR (CD_2Cl_2, 50 MHz): δ 44.3 (C-6), 45.5 (N(3)CH_2), 49.9 (N(7)CH_2), 52.1 (N(1)CH_2), 102.5 (C-5), 126.2-128.4 (CH in Ph), 133.3 (C-8), 134.8 and 136.6 (C in Ph), 138.4 (C-4), 138.8 (C in Ph), 152.3 (C-2). MS (EI): 408 (100, M^+), 397 (2), 385 (2), 368 (2), 361 (3), 350 (2), 344 (2), 336 (5), 331 (8), 319 (100); Hrms calcd for $C_{26}H_{24}N_4O$: 408.1950; found 408.1930.

1,3,7-Tribenzylxanthine (9). Solid 1,3,6,7-tetrahydro-1,3,7-tribenzyl-2H-purin-2-one (85 mg, 0.21 mmol) was exposed to air for 60 days and the product was isolated by flash chromatography eluting with EtOH/$CHCl_3$ (1:49) followed by EtOH/$CHCl_3$ (1:24); yield 40 mg (45 %), colourless crystals. M.p. 117 - 121 °C. ^{1}H NMR (CD_2Cl_2, 200 MHz): δ 5.16, 5.25 and 5.49 (s, 2H, CH_2), 7.2-7.5 (m, 15H, Ph), 7.58 (s, 1H, H-8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 44.8, 46.9 and 50.6 (CH_2), 106.8 (C-5), 126.8-128.4 (CH in Ph), 134.3, 135.6 and 136.5 (C in Ph), 140.1 (C-8), 147.8 (C-4), 150.4 (C-6), 154.1 (C-2). MS (EI): 422 (100, M^+), 405 (2), 394 (2), 383 (2), 355 (3), 331 (20), 317 (4); Hrms calcd for $C_{26}H_{24}N_4O_2$: 422.1743; found 422.1751.

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