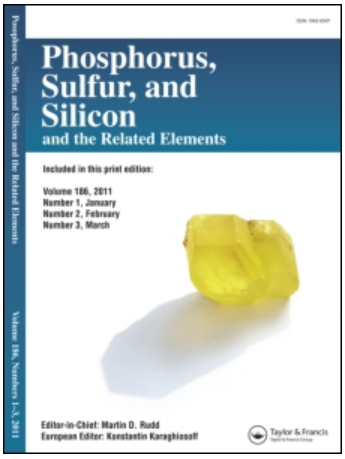

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Silica Sulfuric Acid (SSA) as a Highly Efficient Heterogeneous Catalyst for Persilylation of Purine and Pyrimidine Nucleobases and Other *N*-Heterocycles Using Hmds

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Online publication date: 25 August 2010

To cite this Article Rad, Mohammad Navid Soltani , Khalafi-Nezhad, Ali , Divar, Masoumeh and Behrouz, Somayeh(2010) 'Silica Sulfuric Acid (SSA) as a Highly Efficient Heterogeneous Catalyst for Persilylation of Purine and Pyrimidine Nucleobases and Other *N*-Heterocycles Using Hmds', Phosphorus, Sulfur, and Silicon and the Related Elements, 185: 9, 1943 — 1954

To link to this Article: DOI: 10.1080/10426500903383952

URL: http://dx.doi.org/10.1080/10426500903383952

Phosphorus, Sulfur, and Silicon, 185:1943–1954, 2010

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500903383952

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SILICA SULFURIC ACID (SSA) AS A HIGHLY EFFICIENT HETEROGENEOUS CATALYST FOR PERSILYLATION OF PURINE AND PYRIMIDINE NUCLEOBASES AND OTHER *N*-HETEROCYCLES USING HMDS

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Purine and pyrimidine nucleobases and other* N*-heterocycles have been silylated with HMDS in excellent yields in the presence of a catalytic amount of silica sulfuric acid (SSA) as a heterogeneous catalyst. SSA utilizes a shorter reaction time and higher yields of silylated nucleobases. SSA is reusable for several times without a decrease in reactivity or yield of silylated adducts.

Keywords HMDS; nucleobase; persilylation; silica sulfuric acid (SSA)

INTRODUCTION

Trimethylsilylation of organic compounds having labile hydrogen atoms is finding increasing use in analytical and in preparative organic chemistry.[1] It is a frequently used protection method in multistep synthesis due to its enhanced stability under a variety of conditions, solubility in nonpolar solvents, thermal stability, and the ease of removal of the protecting group, which is simply carried out by acid- or base-induced hydrolysis, giving only unreactive siloxane as a byproduct. Several silylating agents such as chlorotrimethylsilane,[2] hexamethyldisiloxane,[3] *N*-(trimethylsilyl) imidazoles,[4] and ethyl(trimethylsilyl) acetate[5] have been used for the introduction of a trimethylsilyl group onto hydrogen labile hydroxyl and thio substrates. Hexamethyldisilazane (HMDS), as a stable, cheap, and commercially available reagent,[6,7] has been frequently used for this purpose. HMDS handling is easy, and its workup from the reaction mixture is rarely time consuming; however, the low

Received 12 July 2009; accepted 2 October 2009.
We wish to thank the Shiraz University of Technology and Shiraz University Research Councils for partial support of this work.
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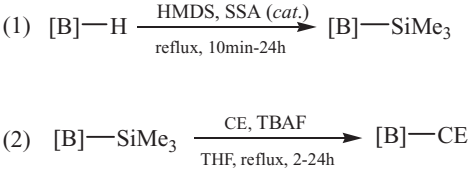
silylating power of HMDS is the main drawback for its application.[8] Therefore, a variety of catalysts have been reported for the activation of HMDS.[9–16]

Acyclic nucleosides constitute a special class of nucleoside analogues, which have attracted great interest due to their broad spectrum of antiviral and anticancer activities.[17] The most common route into nucleoside synthesis involves the *N*-alkylation of nucleobases with various carbon electrophiles.[18–23] The *N*-alkylation of purine and pyrimidine nucleobases is often achieved using two general methods: so-called direct[18–23] and persilylated[24] methods.

The former method has several drawbacks, including low solubility of nucleobases, especially that of purine nucleobases in organic solvents, lack of regioselectivity in the case of ambident nucleobase, low yields of products, harsh reaction condition, tedious workup, and cumbersome separation process. The latter method possesses the apparent advantages of remarkable increment in solubility of nucleobase in organic solvents, enhancement in regioselectivity of the *N*-alkylation site, higher yields of products, milder reaction conditions, and easier workup procedure. Many silylating reagents are used for silylation of hydroxyl compounds such as phenols and alcohols, but HMDS is the most common silylating agent used for nucleobases. Due to the weak silylating power of HMDS and less nucleophilic behavior of nucleobases, the reaction of HMDS with nucleobases requires efficient Lewis or Brønsted acid catalysts. Up to now, ammonium sulfate and/or TMSCl[24] combined with HMDS have been widely employed for the silylation of nucleobases. However, the employment of these acid catalysts is usually accompanied with several limitations and drawbacks. For example, $(NH_4)_2SO_4$ and TMSCl are quite sensitive to moisture and could decompose during prolonged reflux conditions. Additionally, they are nonrecoverable and nonreusable. Furthermore, these catalysts do not efficiently convert the nucleobases to their corresponding silyl ethers, especially in the case of purine derivatives, even if the reaction time is prolonged. Hence finding an efficient heterogeneous Lewis or Brønsted acids catalyst to establish a facile and effective method for silylation of nucleobases is an interesting challenge.

Silica sulfuric acid (SSA) is a heterogeneous acid that currently is largely used for many organic transformations as a solid acid catalyst under various conditions.[25] The wide application of SSA is due to its strong acidity, chemical and thermal stabilities, low cost, reusability, ease of handling, and environmentally benign nature with fewer disposals problems. Encouraged by suitable performance and usefulness of SSA in organic synthesis, and also in continuation of our interest in design and synthesis of novel carboacyclic nucleosides,[18–20,26,27] in this article we report SSA as a highly efficient solid acid catalyst for presilylation of nucleobases as well as the other *N*-heterocycles using HMDS (Scheme 1).



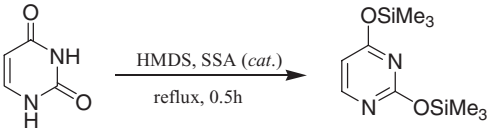
B : purin, pyrimidine nucleobases &, *N*-heterocycles
CE : carbon electrophile

Scheme 1

In the second part of this work, to demonstrate the efficiency of SSA and HMDS for silylation of nucleobases, the presilylated nucleobases attained by this method were condensed with various sources of carbon electrophiles to produce various carboacyclic nucleosides (Scheme 1).

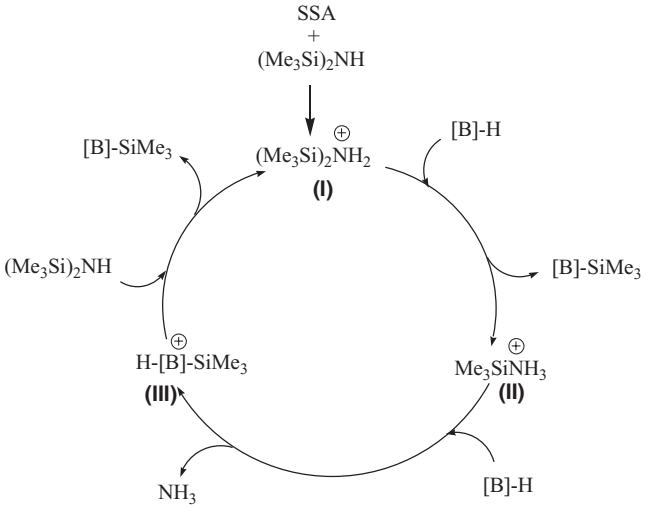
RESULTS AND DISCUSSION

Initially, silylation of uracil was carried out in the presence of a catalytic amount of SSA (0.05 g, 0.13 mmol) as an active heterogeneous acid catalyst in refluxing HMDS (Scheme 2). Uracil was successfully converted to its corresponding trimethylsilyl ether in quantitative yield in a short reaction time.



Scheme 2

The generality and versatility of this method was demonstrated by extension to various purine and pyrimidine nucleobases and other *N*-heterocycles (Table I). As the results in Table I indicate, trimethylsilylation of nucleobases was easily carried out in the presence of SSA in refluxing HMDS in almost quantitative yields. The depicted data in Table I indicate this method is highly efficient and suitable for pyrimidine (Table I, entries 1–4) and purine nucleobases and/or purine-like scaffolds (Table I, entries 5–9). Interestingly, guanine as the most unreactive and insoluble purine nucleobase was efficiently converted to its corresponding trimethylsilyl ether (Table I, entry 6) after refluxing for 24 h.



Scheme 3

Table I Silylation of pyrimidine and purine nucleobases and other *N*-heterocycles using SSA/HMDS

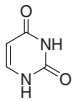
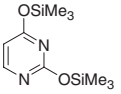
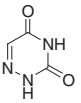
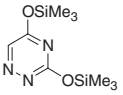
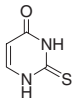
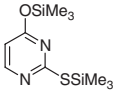
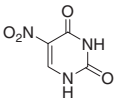
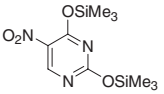
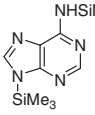
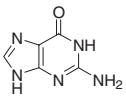
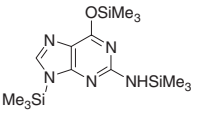
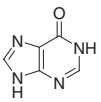
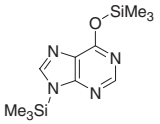
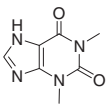
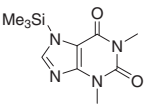
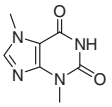
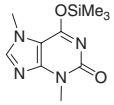
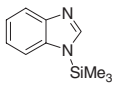
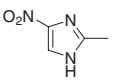
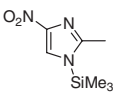
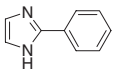
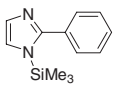
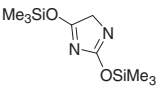
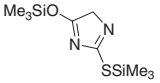
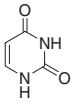
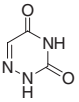
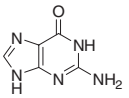
Entry	Substrate	Product	Time (h)	Yield[a] (%)
1			0.5	100
2			0.5	100
3			2	100
4			0.5	100
5			3	100
6			24	90
7			1.5	100
8			1	100
9			2	100
10			0.5	100
11			2	100
12			0.16	100
13			0.5	100

Table I Silylation of pyrimidine and purine nucleobases and other *N*-heterocycles using SSA/HMDS *(Continued)*

Entry	Substrate	Product	Time (h)	Yield[a] (%)
14			0.33	100
15			2	100

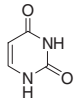
[a]GC yield.

Table II Comparison of some of the results obtained by silylation of nucleobases and other *N*-heterocycles with HMDS in the presence of SSA, TMSCl, and $(NH_4)_2SO_4$

		Time (h)/Yield[a] (%)		
Entry	Substrate	SSA	TMSCl	$(NH_4)_2SO_4$
1		0.5/100	3.5/100	2/100
2		0.5/100	4/100	2/100
3		3/100	24/80	12/95
4		24/90	48/50	80/63
5		0.5/100	0.66/100	1/100
6		0.16/100	0.5/100	0.75/100

[a]GC yield.

Table III The reusability of SSA for presilylation of uracil and adenine

		Time (h)/Yield[a] (%)				
Entry	Substrate	1	2	3	4	5
1		0.5/100	0.67/100	1/95	1.67/91	1.25/88
2		3/100	3.33/100	3.75/94	4.17/86	4.5/82

[a]GC yield.

Table IV *N*-Alkylated nucleobases and other *N*-heterocycles

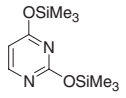
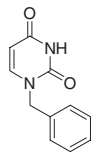
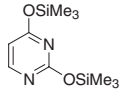
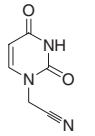
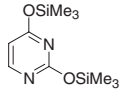
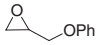
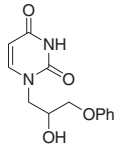
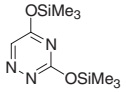
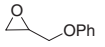
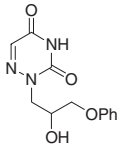
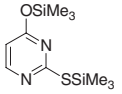
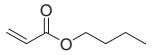
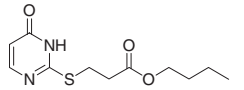
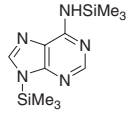
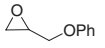
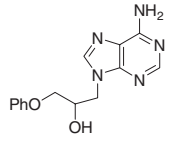
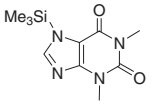
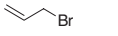
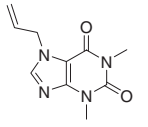
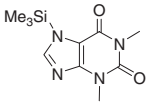
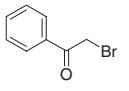
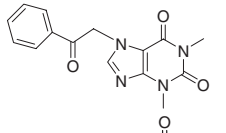
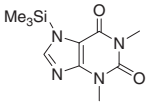
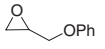
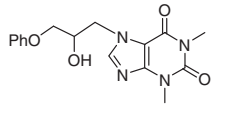
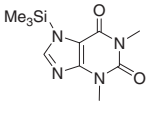
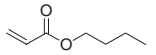
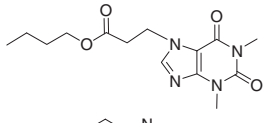
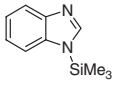
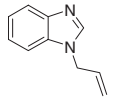
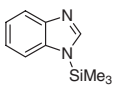
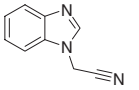
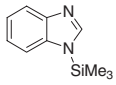
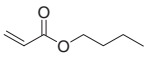
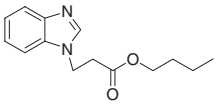
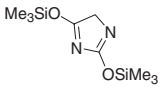
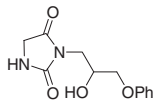
Entry[Ref.]	Substrate	Electrophile	Product	Mp (°C)	Yield[a] (%)
1				167	85
2				180	85
3[19]				156	87
4[19]				Oil	80
5				80	85
6				137	80
7[27]				104	75
8				188	90
9				129	87
10				58	90
11				oil	80

Table IV *N*-Alkylated nucleobases and other *N*-heterocycles *(Continued)*

Entry[Ref.]	Substrate	Electrophile	Product	Mp (°C)	Yield[a] (%)
12				58	90
13				114	90
14				130	90

[a]Isolated yield.

Additionally, the optimized conditions were also applied to other *N*-heterocycles, including benzimidazole, 2-methyl-4-nitro-1*H*-imidazole, imidazole, 2-phenyl imidazole, hydantoin, and thiohydantoin (Table I, entries 10–15).

To demonstrate the efficiency of the present method, we compared some of our results using SSA with those attained by TMSCl and $(NH_4)_2SO_4$ (Table II). As the data in Table II indicate, higher yields of silylated nucleobases and/or shorter reaction times were obtained when SSA was used.

The reusability of the catalyst was tested in presilylation of uracil and adenine (Table III). As shown in Table III, the catalyst was recovered after each run, washed three times with acetone, dried in a vacuum oven at 100°C for 30 min prior to use, and tested for its activity in the subsequent run and fresh catalyst was not added. The catalyst was tested for five runs. It was seen that the catalyst displayed favorable reusability.

The mechanism of the reaction is not clear; however on the basis of our observations related to the fast evolution of NH_3 gas from the reaction mixture and the reusability of the catalyst without any considerable loss of its catalytic activity, we have proposed a mechanism that is shown in Scheme 3.[9]

On the basis of this mechanism, acid–base interaction between SSA and HMDS polarizes the Si-N bond in HMDS to produce the reactive silylating agent (**I**). A reaction of purine and pyrimidine nucleobases as well as other *N*-heterocycles with (**I**) results in the formation of ammonium silylating species (**II**) with concomitant release of the corresponding silyl ether. Irreversible cleavage of (**II**) with a nucleobase or other *N*-heterocycles leads to the fast evolution of NH_3 and also formation of the unstable protonated silyl ether (**III**). Release of H^+ as catalyst from intermediate (**III**) re-enters catalytic cycle (Scheme 3).

To demonstrate the effectiveness of SSA in the persilylation reaction of nucleobases, the silyl ethers of nucleobases as well as other *N*-heterocycles prepared by present method were condensed with different sources of carbon electrophiles including alkyl halides, epoxides, and Michael acceptors by using tetra-*n*-butylammonium fluoride (TBAF) as a desilylating agent (Scheme 1). The structures of the synthesized compounds are shown in Table IV. As the data in Table IV indicate, high yields of corresponding acyclic nucleosides were attained. The good yield of acyclic nucleosides is evidence for efficient persilylation of nucleobases using SSA.

CONCLUSION

In summary, a convenient method for trimethylsilylation of various nucleobases and other *N*-heterocycles using SSA and HMDS has been established. SSA has proven to be an efficient heterogeneous acid catalyst for presilylation of nucleobases and showed a favorable reusability after many runs. Higher yields of the silyl ethers, shorter reaction times, and easier workup procedure are the main advantages of the described method.

EXPERIMENTAL

All reagents were purchased from Merck and Fluka and were used without further purification. The progress of the reactions was followed with TLC using silica gel SILG/UV 254 plates. Silica gel 60, 0.063–0.200 mm (70–230 mesh ASTM) was used for column chromatography. IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) spectra were run on a Brüker Avanced DPX-250 FT-NMR spectrometer, δ in ppm, J in Hz. GC analysis was run with Shimadzu GC-14A. Melting points (mp) were recorded on a Büchi 510 apparatus in open capillary tubes and are uncorrected.

Preparation of Silica Sulfuric Acid

SSA was prepared by the method described in the literature.[28]

Typical Procedure for SSA-Catalyzed Silylation of Nucleobases and Other N-Heterocycles in the Presence of HMDS

In a 250-mL round-bottom flask, a mixture of the appropriate nucleobase or other *N*-heterocycle (10 mmol), SSA (0.05 g), and HMDS (100 mL) was heated at reflux until a clear solution was obtained (Table I). Then the catalyst was filtered off, and the filtrate was evaporated under vacuum to remove the solvent (HMDS). The resulting crude was pure enough as indicated by GC analysis to be used for any synthetic application and does not require further purification or characterization.

Typical Procedure for N-Alkylation of Silylated Nucleobases and Other N-Heterocycles

To a double-necked 250-mL round-bottom flask equipped with a condenser containing an appropriate amount of persilylated nucleobase (0.01 mol) and electrophile (15 mmol) diluted in freshly distilled, anhydrous THF (100 mL), anhydrous TBAF (2.62 g, 10 mmol) in THF solution (20 mL) was gradually added over 20 min. Then, the mixture was heated at reflux (TLC control). The solvent was evaporated at reduced pressure, and the residue was dissolved in $CHCl_3$ (200 mL) and washed with H_2O (3 $\times$ 100 mL). The organic layer was dried (10 g of Na_2SO_4) and concentrated to afford the crude product.

Spectral Data for1-Benzylpyrimidine-2,4(1*H*,3*H*)-dione (Table III, Entry 1)

Purification by column chromatography on silica gel using EtOAc/*n*-hexane (1:1) afforded white crystals (1.7 g, 85%). Mp = 167°C. R_f (EtOAc/*n*-hexane 1:1) (0.66). IR

(KBr) cm^{-1}: 3350, 3089, 2855, 1730, 1705. δ_H (250 MHz, DMSO-d_6) 11.53 (1H, s, NH exchangeable with D_2O), 7.71 (1H, d, $J = 7.8$ Hz, C(6)—H), 7.35–7.26 (5H, m, Ph), 5.58 (1H, d, $J = 7.8$ Hz, C(5)—H), 4.86 (2H, s, CH_2). δ_C (62.5 MHz, DMSO-d_6) 163.68, 150.99, 145.57, 136.79, 128.58, 127.59, 127.35, 101.31, 50.23. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85%. Found: C, 65.30; H, 4.91; N, 13.94%.

Spectral Data for 2-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetonitrile (Table IV, Entry 2)

Purification by column chromatography on silica gel using EtOAc/*n*-hexane (1:1) afforded white crystals (1.2 g, 85%). Mp = 180°C. R_f (EtOAc/*n*-hexane 1:1) (0.68). IR (KBr) cm^{-1}: 3300, 3080, 2842, 2195, 1725, 1700. δ_H (250 MHz, DMSO-d_6) 11.48 (1H, s, NH exchangeable with D_2O), 7.51 (1H, d, $J = 7.7$ Hz, C(6)—H), 5.66 (1H, d, $J = 7.7$ Hz, C(5)—H), 4.74 (2H, s, CH_2). δ_C (62.5 MHz, DMSO-d_6) 161.93, 150.49, 141.79, 115.93, 99.31, 27.48. Anal. Calcd for $C_6H_5N_3O_2$: C, 47.69; H, 3.33; N, 27.81%. Found: C, 47.72; H, 3.38; N, 27.75%.

Spectral Data for Butyl 3-(6-Oxo-1,6-dihydropyrimidin-2-ylthio)propanoate (Table IV, Entry 5)

Purification by column chromatography on silica gel using EtOAc/*n*-hexane (1:2) afforded white crystals (2.1 g, 85%). Mp = 80°C. R_f (EtOAc/*n*-hexane 1:2) (0.58). IR (KBr) cm^{-1}: 3200, 3050, 2895, 1750, 1725, 1300. δ_H (250 MHz, DMSO-d_6) 12.54 (1H, s, NH exchangeable with D_2O), 7.84 (1H, d, $J = 6.5$ Hz, C(6)—H), 6.08 (1H, d, $J = 6.5$ Hz, C(5)—H), 4.00 (2H, t, $J = 6.4$ Hz, OCH_2), 3.26 (2H, t, $J = 6.6$ Hz, SCH_2), 2.71 (2H, t, $J = 6.6$ Hz, O=CCH_2), 1.55–1.47 (2H, m, CH_2), 1.34–1.25 (2H, m, CH_2), 0.83 (3H, t, $J = 7.2$ Hz, CH_3). δ_C (62.5 MHz, DMSO-d_6) 175.96, 171.21, 153.70, 146.44, 109.61, 63.82, 33.58, 30.07, 24.96, 18.52, 13.43. Anal. Calcd for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93; S, 12.51%. Found: C, 51.58; H, 6.33; N, 10.90; S, 12.55%.

Spectral Data for 1-(6-Amino-9*H*-purin-9-yl)-3-phenoxypropan-2-ol (Table IV, Entry 6)

Purification by column chromatography on silica gel using EtOAc/*n*-hexane (1:2) afforded white crystals (2.2 g, 80%). Mp = 137°C. R_f (EtOAc/*n*-hexane 1:2) (0.53). IR (KBr) cm^{-1}: 3500, 3350, 3090, 1350, 1300, 1050. δ_H (250 MHz, DMSO-d_6) 8.42 (1H, s, C(8)—H), 8.30 (1H, s, C(2)—H), 7.51–7.45 (5H, m, Ph), 7.14 (2H, br s, NH, exchangeable with D_2O), 4.47 (1H, s, OH, exchangeable with D_2O), 4.44–4.38 (1H, m, CH), 4.30 (2H, dd, $J = 3.7$, 10.2 Hz), 4.14 (2H, dd, $J = 6.2$,10.2 Hz). δ_C (62.5 MHz, DMSO-d_6) 158.56, 156.32, 152.76, 150.05, 141.92, 129.85, 121.11, 119.09, 114.64, 70.07, 69.48, 46.72. Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55%. Found: C, 58.97; H, 5.24; N, 24.59%.

Spectral Data for 1,3-Dimethyl-7-(2-oxo-2-phenyl-ethyl)-3,7-dihydro-purine-2,6-dione (Table IV, Entry 8)

Purification by column chromatography on silica gel using EtOAc/*n*-hexane (1:2) afforded white crystals (2.6 g, 90%). Mp = 188°C. R_f (EtOAc/*n*-hexane 1:2) (0.60). IR

(KBr) cm^{-1}: 3085, 2910, 1725, 1715, 1705. δ_H (250 MHz, $CDCl_3$) 7.98–7.95 (2H, m, Ph), 7.62 (1H, s, C(8)—H), 7.52–7.46 (3H, m, Ph), 5.77 (2H, s, NCH_2), 3.58 (3H, s, N-Me), 3.30 (3H, s, N-Me). δ_C (62.5 MHz, $CDCl_3$) 191.12, 155.34, 151.54, 148.43, 142.37, 134.39, 133.85, 129.00, 128.04, 107.02, 51.81, 29.72, 27.74. Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78%. Found: C, 60.49; H, 4.70; N, 18.72%.

Spectral Data for 7-(2-Hydroxy-3-phenoxypropyl)-1,3-dimethyl-1*H*-purine-2,6(3H,7H)-dione (Table IV, entry 9)

Purification by column chromatography on silica gel using EtOAc/*n*-hexane (1:2) afforded white crystals (2.8 g, 87%). Mp = 129°C. R_f (EtOAc/*n*-hexane 1:2) (0.69). IR (KBr) cm^{-1}: 3500, 3100, 2943, 1725, 1710, 1303, 1055. δ_H (250 MHz, $CDCl_3$) 7.66 (1H, s C(8)—H), 7.32–7.25 (2H, m, Ph), 7.01–6.87 (3H, m, Ph), 4.65 (2H, dd, J = 2.5, 13.4 Hz, OCH_2), 4.51–4.48 (1H, m, CH), 4.18 (1H, s, OH exchangeable with D_2O), 4.07–3.95 (2H, dd, J = 3.5, 13.4 Hz, NCH_2), 3.56 (3H, s, N-Me), 3.37 (3H, s, N-Me). δ_C (62.5 MHz, $CDCl_3$) 158.04, 155.59, 151.29, 148.75, 142.66, 129.49, 121.36, 114.35, 106.97, 68.82, 68.68, 49.65, 29.76, 27.96. Anal. Calcd for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96%. Found: C, 58.24; H, 5.45; N, 16.98%.

Spectral Data for Butyl 3-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-yl)propanoate (Table IV, Entry 10)

Purification by column chromatography on silica gel using EtOAc/*n*-hexane (1:2) afforded white crystals (2.7 g, 90%). mp = 58°C. R_f (EtOAc/*n*-hexane 1:2) (0.59). IR (KBr) cm^{-1}: 3085, 2895, 1730, 1718, 1704, 1350, 1310. δ_H (250 MHz, $CDCl_3$) 7.59 (1H, s, C(8)—H), 4.40 (2H, t, J = 6.5 Hz, OCH_2), 3.89 (2H, t, J = 6.1 Hz, NCH_2), 3.43 (3H, s, N-Me), 3.25 (3H, s, N-Me), 2.80 (2H, t, J = 6.1 Hz, O=CCH_2), 1.49–1.37 (2H, m, CH_2), 1.25–1.13 (2H, m, CH_2), 0.73 (3H, t, J = 7.30 Hz, CH_3). δ_C (62.5 MHz, $CDCl_3$) 170.70, 154.95, 151.47, 148.92, 142.08, 106.40, 64.78, 42.57, 34.78, 30.36, 29.62, 27.81, 18.90, 13.50. Anal. Calcd for $C_{14}H_{20}N_4O_4$: C, 54.54; H, 6.54; N, 18.17%. Found: C, 54.62; H, 6.51; N, 18.23%.

Spectral Data for 1-Allyl-1*H*-benzo[d]imidazole (Table IV, Entry 11)

Purification by column chromatography on silica gel using EtOAc/*n*-hexane (1:2) afforded a colorless oil (1.2 g, 80%). R_f (EtOAc/*n*-hexane 1:2) (0.62). IR (film) cm^{-1}: 3090, 2943, 1350. δ_H (250 MHz, $CDCl_3$) 8.62 (1H, s, C(2)—H), 7.46–7.41 (2H, m, aryl), 6.88–6.82 (2H, m, aryl), 5.43–5.39 (1H, m, =CH), 4.79 (2H, dd, J = 8.4, 16.5 Hz, $=CH_2$), 4.11 (2H, d, J = 5.7 Hz, NCH_2). δ_C (62.5 MHz, $CDCl_3$) 143.55, 142.84, 133.60, 131.79, 122.66, 121.87, 119.86, 118.01, 109.93, 46.88. Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71%. Found: C, 75.95; H, 6.42; N, 17.78%.

Spectral Data for 2-(1*H*-Benzo[d]imidazol-1-yl)acetonitrile (Table IV, Entry 12)

Purification by column chromatography on silica gel using EtOAc/*n*-hexane (1:2) afforded white crystals (2.7 g, 90%). Mp = 58°C. R_f (EtOAc/*n*-hexane 1:2) (0.59). IR

(KBr) cm^{-1}: 3090, 2880, 2200, 1350. δ_H (250 MHz, DMSO-d_6) 8.37 (1H, s, C(2)—H), 7.78–7.61 (2H, m, aryl), 7.39–7.18 (2H, m, aryl), 5.69 (2H, s, NCH_2). δ_C (62.5 MHz, DMSO-d_6) 143.99, 129.12, 122.40, 122.06, 121.84, 119.47, 116.14, 111.17, 46.77. Anal. Calcd for $C_9H_7N_3$: C, 68.78; H, 4.49; N, 26.74%. Found: C, 68.73; H, 4.56; N, 26.72%.

Spectral Data for Butyl 3-(1*H*-Benzo[*d*]imidazol-1-yl)propanoate (Table IV, Entry 13)

Purification by column chromatography on silica gel using EtOAc/*n*-hexane (1:2) afforded white crystals (2.1 g, 90%). Mp = 114°C. R_f (EtOAc/*n*-hexane 1:2) (0.55). IR (film) cm^{-1}: 3088, 2860, 1735, 1350, 1305. δ_H (250 MHz, $CDCl_3$) 7.84 (1H, s, C(2)—H), 7.71–7.67 (2H, m, aryl), 7.29–7.13 (2H, m, aryl), 4.30 (2H, t, J = 6.5 Hz, OCH_2), 3.90 (2H, t, J = 6.7 Hz, NCH_2), 2.69 (2H, t, J = 6.7 Hz, O=CCH_2), 1.47–1.35 (2H, m, CH_2), 1.23–1.09 (2H, m, CH_2), 0.73 (3H, t, J = 7.3 Hz, CH_3). δ_C (62.5 MHz, $CDCl_3$) 170.64, 143.73, 143.31, 133.32, 122.92, 122.11, 120.33, 109.32, 64.93, 40.26, 34.30, 30.36, 18.91, 13.55. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37%. Found: C, 68.29; H, 7.45; N, 11.32%.

Spectral Data for 3-(2-Hydroxy-3-phenoxypropyl)imidazolidine-2,4-dione (Table IV, Entry 14)

Purification by column chromatography on silica gel using EtOAc/*n*-hexane (1:2) afforded white crystals (2.25 g, 90%). Mp = 130°C. R_f (EtOAc/*n*-hexane 1:2) (0.55). IR (KBr) cm^{-1}: 3350, 3200, 3050, 2885, 1715, 1705, 1315, 1057. δ_H (250 MHz, $CDCl_3$) 7.21–7.10 (2H, m, Ph), 6.83 (1H, s, NH, exchangeable with D_2O), 6.80–6.72 (3H, m, Ph), 4.22–4.15 (5H, complex, OCH_2, NCH_2C=O), 3.79 (1H, s, OH, exchangeable with D_2O), 3.56 (2H, dd, J = 6.35, 14.47 Hz, NCH_2). δ_C (62.5 MHz, $CDCl_3$) 171.56, 158.83, 158.48, 129.62, 121.22, 114.50, 70.43, 68.11, 46.48, 42.10. Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19%. Found: C, 57.54; H, 5.71; N, 11.13%.

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