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ORIGINAL PAPER

Chitosan–silica sulfate nanohybrid: a highly efficient and green heterogeneous nanocatalyst for the regioselective synthesis of *N*-alkyl purine, pyrimidine and related *N*-heterocycles via presilylated method

Somayeh Behrouz[1] · **Mohammad Navid Soltani Rad**[1] · **Mohammad Amin Piltan**[1]

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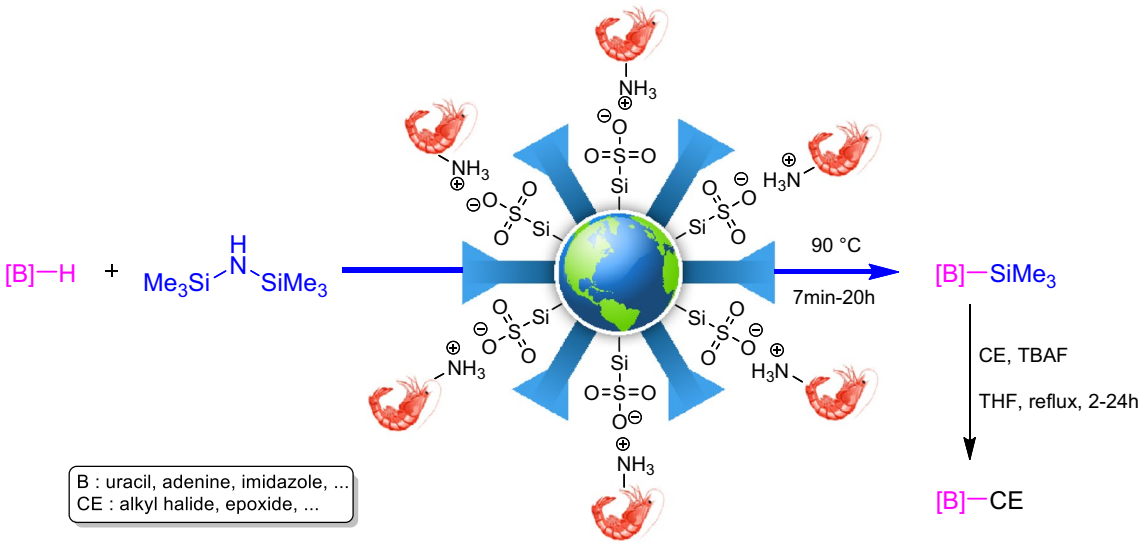
Abstract

The presilylation of purine and pyrimidine nucleobases as well as other related *N*-heterocycles with HMDS utilizing chitosan–silica sulfate nanohybrid (CSSNH) is described. CSSNH is proved to be a useful, highly efficient and eco-friendly heterogeneous nanohybrid catalyst for silylation of nucleobases. The presilylated nucleobases then underwent the reaction with different sources of carbon electrophiles to afford the desired *N*-alkyl-substituted derivatives in good-to-excellent yields. CSSNH exhibits several advantageous involving ease of handling and preparation, low cost, reusability and environmental benignity. These unique properties render the CSSNH to be an ideal candidate for use in green industrial processes.

Graphic abstract



Keywords CSSNH · Heterogeneous nanocatalyst · HMDS · Nucleobase · Presilylation

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✉ Somayeh Behrouz
behrouz@sutech.ac.ir

✉ Mohammad Navid Soltani Rad
soltani@sutech.ac.ir

Extended author information available on the last page of the article

Introduction

The organosilicon derivatives are versatile and important substrates in chemistry. Over the years, the employment of organosilicons is found enormous growth for both synthetic and analytical purposes (Auner and Weis 1994; Lee 2017a, b; Knapp 1979). The silylation of organic compounds are

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extensively applied in multistep synthesis of drugs and natural products, in particular, nucleosides and nucleotides (Auner and Weis 1994; Lee 2017a, b; Knapp 1979; Lukevics et al. 1974). Silylated organic materials are widely applied in analytical techniques such as GC, GLC, MS, GC–MS, and HPLC (Knapp 1979). The incorporation of silyl groups into organic molecules provide numerous benefits such as protection of the desired functional groups, enhancement of chemical stability under different conditions, thermal stability, solubility, and volatility, selective operation, ease of handling and simple removal via basic and/or acidic hydrolysis. The trimethylsilyl (TMS) group is one of the most popular and known silyl groups which were largely used to protect the organic functionalities (Auner and Weis 1994; Lee 2017a, b; Knapp 1979; Lukevics et al. 1974). The numerous trimethylsilylating reagents with different reactivities have been developed so far (Auner and Weis 1994; Lee 2017a, b; Knapp 1979; Lukevics et al. 1974). Among them, hexamethyldisilazane (HMDS) is a very famous reagent owing to its cheapness, low boiling point, high selectivity, ease of handling and workup, stability, and commercial availability (Torkelson and Ainsworth 1976). In addition, HMDS can be used as both silylating agent and solvent that merely release ammonia as a by-product which can leave from the reaction mixture to push the reaction to completion (Torkelson and Ainsworth 1976). Despite multifarious advantages of utilizing HMDS, HMDS exhibits the poor TMS transferring tendency which is the main known drawback for HMDS (Bruynes and Jurrines 1982). To overcome this drawback, different catalysts have been applied in combination with HMDS (Nikbakht et al. 2014; Lee and Kadam 2011; Rostami et al. 2010; Zareyee and Karimi 2007; Rajagopal et al. 2009; Narsaiah 2007; Ko et al. 2014; Ghafuri et al. 2017; Shaterian et al. 2007).While various efficient protocols have been reported so far, plenty of them exhibit one or more disadvantages such as harsh reaction condition, low yield, and prolonged reaction time as well as the use of non-reusable and non-recyclable catalysts.

Nucleoside and their derivatives are extremely important molecules in pharmaceutical chemistry especially due to their extensive applications such as anticancer and antiviral drugs (Kleeman et al. 1999). To obtain the nucleosides, the *N*-alkylation reaction of nucleobases with different sources of carbon electrophiles is a well established and customized method (Khalafi-Nezhad et al. 2004; Soltani Rad et al. 2009a, 2014, 2015; Amblard et al. 2005). To this end, the use of purine and pyrimidine nucleobases in presilylated form rather than their naked shapes affords remarkable benefits such as mild reaction condition, high yield, ease of workup and separation process, regioselectivity at the site of *N*-alkylation, and good solubility in organic solvents (Chu and Cutler 1986). Numerous famous antiviral and anticancer drugs such as acyclovir, cladribine, gemcitabine, stavudine, tegafur, and trifluridine were synthesized by the presilylation of the corresponding purine or pyrimidine nucleobases (Kleeman et al. 1999). HMDS is the most extensively used TMS transfer reagent for silylation of nucleobases. Thanks to marginal nucleophilic power of nucleobases and low silylating ability of HMDS, the use of a potent catalyst is crucial for the reaction to progress efficiently. Traditionally, HMDS/$(NH_4)_2SO_4$ and HMDS/TMSCl (Lukevics et al. 1974; Chu and Cutler 1986; Nishimura and Iwai 1964; Tachallait et al. 2018; Voight et al. 2019) have been mostly used for the silylation of nucleobases. Practically, the high moisture sensitivity, non-recoverability, and non-reusability of $(NH_4)_2SO_4$ and TMSCl as well as their low efficiency in silylation of purine nucleobases have restricted the application of these catalysts. Previously, our group reported the application of silica–sulfuric acid (SSA) as the first heterogeneous catalyst for silylation of nucleobases and other *N*-heterocycles using HMDS (Soltani Rad et al. 2010). Although SSA is a highly proficient heterogeneous catalyst for this purpose, the strong acidity of SSA has restricted its application in the case of acid-sensitive substrates. Consequently, the search for a mild, chemically and thermally stable, cheap, recyclable and eco-friendly heterogeneous catalyst for efficient silylation of nucleobases is still underway.

Natural biopolymers are outstanding substrates from both economic and environmental aspects. Nowadays, many scientists have focused their research activities on the application of natural biopolymers in different areas of sciences. In particular, natural biopolymers have been extensively employed as eco-friendly material to prepare heterogeneous catalysts (Primo et al. 2009; Rovira-Truitt et al. 2009). Chitosan (CS, Fig. 1) is a well-known naturally occurring polysaccharide which has gained increasing applications in numerous scientific and industrial fields owing to its unique properties (Honarkar and Barikani 2009). Additionally, chitosan is widely present in industrial waste which can be easily prepared from alkaline deacetylation of chitin from crustaceans (Aranaz et al. 2009). Chitosan is a biocompatible, biodegradable, very cheap, inert towards air and moisture, hydrophilic, chemically reactive, and non-toxic naturally occurring biosolid (Honarkar and Barikani 2009). Due to the presence of amine and hydroxyl functional groups in the chitosan scaffold, this biopolymer can easily undergo chemical modifications and also afford appropriate chelating properties (Honarkar and Barikani 2009; Nasir Baig et al. 2014; Rai et al. 2004; Zarnegar and Safari 2014; Ahmed and Siddiqui 2015; Shen et al. 2014; Molnár 2019).

In recent decades, the (bio)organic–inorganic hybrid materials have been a subject of research interest in different aspects of science (Nalwa 2003). Practically, these hybrid materials have found numerous applications in various areas such as medicine, chemistry, bio(techno)logy, tissue engineering, photonic, cosmetics, electronics, energy, coatings,

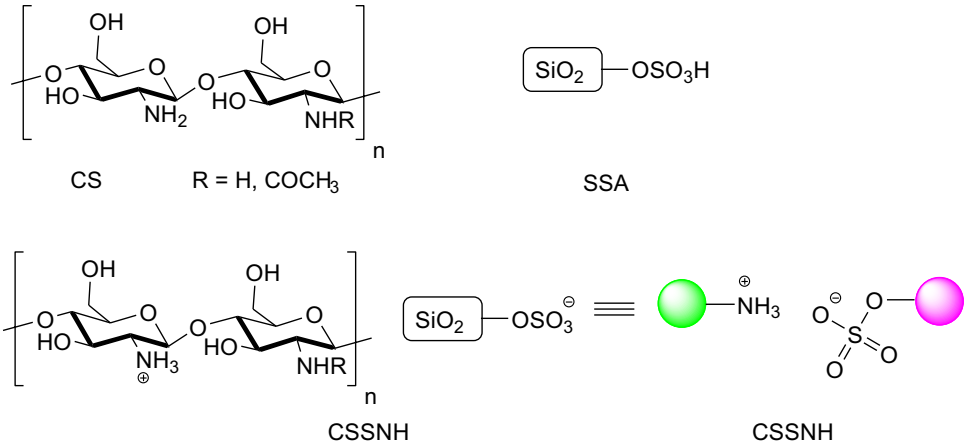
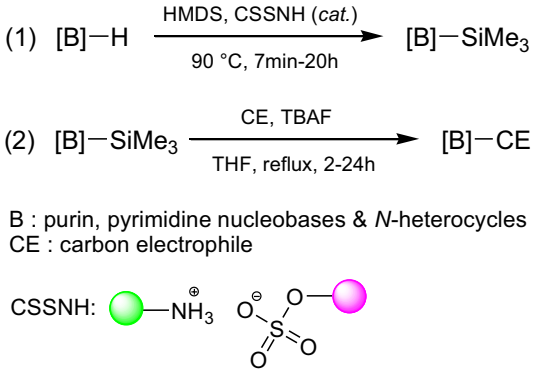


Fig. 1 The general structure of chitosan (CS), silica–sulfuric acid (SSA) and chitosan–silica sulfate nanohybrid (CSSNH)



Scheme 1 Synthesis of *N*-alkyl purine, pyrimidine and other *N*-heterocycles via presilylated method

dyes and pigments (Nalwa 2003; Bucur et al. 2017; Um et al. 2017; Kaushik et al. 2015; Vallet-Regí et al. 2011). Indeed, the biopolymers can be usefully applied to the preparation of biopolymer–inorganic hybrid catalysts to afford the new environmentally benign catalysts. In this context, the immobilized chitosan or chitosan–metal complexes on the surface of porous silica gel have been employed in several organic transformations (Guibal 2005). Along this line, we recently reported the synthesis and characterization of chitosan–silica sulfate nanohybrid (CSSNH) as a novel, green, eco-friendly, highly efficient and inexpensive heterogeneous nanocatalyst. CSSNH was successfully employed in the synthesis of thiiranes from epoxides (Behrouz et al. 2018) and 1,2-diol mono-esters via regioselective ring opening reaction of epoxides with carboxylic acids (Behrouz et al. 2017). In another attempt to discover the new applications for CSSNH and also in continuation of our ongoing research interest in developing new synthetic protocols for the synthesis of *N*-alkyl nucleobases, we now report CSSNH as a highly efficient and green biopolymer–inorganic hybrid nanocatalyst for the presilylation of nucleobases and other *N*-heterocycles in HMDS at 90 °C (Scheme 1). To ascertain the efficiency of CSSNH and HMDS for silylation of nucleobases, these presilylated nucleobases were then coupled with different carbon electrophiles to afford the various acyclic nucleosides in good-to-excellent yields (Scheme 1).

Experimental

General

All chemicals were purchased from Merck or Sigma-Aldrich. CSSNH was prepared as per the reported procedure (Behrouz et al. 2018). Solvents were purified by standard procedures, and stored over 3 Å molecular sieves. Reactions were followed by TLC using SILG/UV 254 silica gel plates. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, 70–230 mesh; ASTM). ^{1}H- and ^{13}C-NMR spectrum was recorded on Brüker Avance-DPX-250/400 spectrometer operating at 250/62.5 MHz, respectively. Chemical shifts are given in δ relative to tetramethylsilane (TMS) as an internal standard; coupling constants J are given in Hz. GC–MS was performed on a Shimadzu GC/MS-QP 1000-EX apparatus (m/z; rel. %). IR spectra were obtained using a Shimadzu FT-IR-8300 spectrophotometer. Elemental analyses were performed on a PerkinElmer 240-B micro-analyzer. Melting points were measured using Electrothermal IA 9000 melting point apparatus in open capillary tubes and are uncorrected.

General procedure for silylation of nucleobases or other *N*-heterocycles using CSSNH

To a round-bottom flask (50 mL) was added a mixture of the desired nucleobases or other *N*-heterocycles (1 mmol), CSSNH (0.05 g), and HMDS (10 mL). The reaction mixture was heated at 90 °C until a clear liquid was attained (Table 3). Subsequently, the catalyst was filtered and the filtrate was then evaporated using vacuum to separate the crude silylated

product from HMDS. The crude product was pure enough to be applied in the next step without further purification.

General procedure for *N*-alkylation of silylated nucleobases or other related *N*-heterocycles

To a double-necked round-bottom flask (250 mL) equipped with a condenser was added a mixture of the desired silylated nucleobase (10 mmol), an appropriate electrophile (13 mmol), anhydrous THF (80 mL), and anhydrous TBAF (10 mmol). The reaction mixture was heated at reflux until TLC monitoring indicated no further progress of the reaction. Afterward, the reaction mixture was evaporated under vacuum to remove the solvent. The residue was then dissolved in $CHCl_3$ (100 mL) and washed with H_2O (3 × 100 mL). The organic layer was dried using Na_2SO_4 and evaporated to afford the crude product. The crude was purified by column chromatography on silica gel eluted with proper solvent.

Recycling the catalyst

After completion of the reaction (Table 3), CSSNH was vacuum-filtered and separated from the reaction mixture using a sintered glass funnel and washed with hot THF (2 × 3 mL). Afterward, the catalyst was dried in vacuum oven at 50°C for 2 h. The recovered CSSNH was then employed in the next silylation reaction without further purification.

Data for synthesized compounds

1-(2-(4-Chlorophenoxy)ethyl)pyrimidine-2,4(1*H*,3*H*)-dione (entry 1)

Column chromatography on silica gel eluted with hexane/EtOAc (1:1) afforded pure product as white solid (2.29 g, 86%); m.p. 216–217 °C. IR (KBr): 3200, 3041, 2949, 2871, 1725, 1712, 1492, 1236, 1039 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 4.08 (t, J = 4.8 Hz, 2H, NCH_2), 4.20 (t, J = 4.8 Hz, 2H, OCH_2), 5.57 (d, J = 7.8 Hz, 1H, C(5)–H of uracil), 6.96 (d, J = 8.9 Hz, 2H, aryl), 7.32 (d, J = 8.9 Hz, 2H, aryl), 7.71 (d, J = 7.8 Hz, 1H, C(6)–H of uracil), 11.34 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 46.78, 65.54, 100.61, 116.18, 124.62, 129.19, 146.15, 150.90, 156.77, 163.67. MS (EI): m/z (%) = 266 (27.2) [M^+]. Anal. Calc. for $C_{12}H_{11}ClN_2O_3$: C, 54.05; H, 4.16; N, 10.50; found: C, 53.84; H, 4.28; N, 10.31.

1-(4-Methoxybenzyl) pyrimidine-2, 4(1*H*,3*H*)-dione (entry 2, Soltani Rad et al. 2009b)

Column chromatography on silica gel eluted with hexane/EtOAc (1:1) afforded pure product as white solid (2.09 g, 90%); m.p. 118–119 °C. IR (KBr): 3250, 3100, 2895, 1728, 1715, 1456, 1248 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 3.70 (s, 3H, OCH_3), 4.76 (s, 2H, NCH_2), 5.58 (d, J = 7.8 Hz, 1H, C(5)–H of uracil), 6.84 (d, J = 8.6 Hz, 2H, aryl), 7.14 (d, J = 8.6 Hz, 2H, aryl), 7.72 (d, J = 7.8 Hz, 1H, C(6)–H of uracil), 11.17 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 49.66, 54.99, 101.19, 113.55, 128.67, 129.12, 145.38, 150.95, 158.79, 163.62. MS (EI): m/z (%) = 232 (16.5) [M^+]. Anal. Calc. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06; found: C, 62.14; H, 5.34; N, 12.21.

1-(3-(4-Chlorophenoxy)propyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (entry 3)

Column chromatography on silica gel eluted with hexane/EtOAc (1:1) afforded pure product as white solid (2.56 g, 87%); m.p. 169–170 °C. IR (KBr): 3151, 3075, 2867, 2806, 1730, 1718, 1456, 1247, 1052 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 1.73 (s, 3H, CH_3), 2.03–2.10 (m, 2H, OCH_2CH_2), 3.82 (t, J = 6.7 Hz, 2H, NCH_2), 4.00 (t, J = 5.8 Hz, 2H, OCH_2), 6.94 (d, J = 8.9 Hz, 2H, aryl), 7.33 (d, J = 8.9 Hz, 2H, aryl), 7.62 (s, 1H, C(6)–H of thymine), 11.24 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 11.83, 27.83, 44.94, 65.36, 108.34, 116.05, 124.21, 129.09, 141.49, 150.87, 157.14, 164.26. MS (EI): m/z (%) = 294 (29.4) [M^+]. Anal. Calc. For $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; N, 9.50; found: C, 57.18; H, 5.29; N, 9.71.

Butyl 3-(6-oxo-1,6-dihydropyrimidin-2-ylthio)propanoate (entry 4, Soltani Rad et al. 2010)

Column chromatography on silica gel eluted with hexane/EtOAc (1:1) afforded pure product as white solid (2.18 g, 85%); m.p. 80–81 °C. IR (KBr): 3200, 3050, 2895, 1750, 1725, 1710, 1300, 1240 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 0.83 (t, J = 7.2 Hz, 3H, CH_3), 1.25–1.34 (m, 2H, CH_3CH_2), 1.47-1.55 (m, 2H, OCH_2CH_2), 2.71 (t, J = 6.6 Hz, 2H, $O{=}CCH_2$), 3.26 (t, J = 6.6 Hz, 2H, SCH_2), 4.00 (t, J = 6.4 Hz, 2H, OCH_2), 6.08 (d, J = 6.5 Hz, 1H, C(5)–H of thiouracil), 7.84 (d, J = 6.5 Hz, 1H, C(6)–H of thiouracil), 12.54 (s, 1H, NH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 13.43, 18.52, 24.96, 30.07, 33.58, 63.82, 109.61, 146.44, 153.70, 171.21, 175.96. MS (EI): m/z (%) = 256 (16.8) [M^+]. Anal. Calc. for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93; found: C, 51.65; H, 6.42; N, 11.05.

9-(2-(4-Benzylphenoxy)ethyl)-9*H*-purin-6-amine (entry 5)

Column chromatography on silica gel eluted with EtOAc afforded pure product as yellow solid (2.83 g, 82%); m.p.

201–202 °C. IR (KBr): 3332, 3109, 3010, 2929, 2875, 1595, 1487, 1242, 1047 cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 3.81 (s, 2H, NH_2, exchangeable with D_2O), 4.29 (t, J = 4.9 Hz, 2H, NCH_2), 4.49 (t, J = 4.9 Hz, 2H, OCH_2), 6.82 (s, 2H, PhCH_2), 7.05–7.25 (complex, 10 H, aryl, C(2)–H of adenine), 8.14 (s, 1H, C(8)–H of adenine). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 40.11, 42.48, 65.58, 114.43, 118.58, 125.76, 128.29, 128.48, 129.64, 133.72, 141.10, 141.56, 149.47, 152.40, 155.90, 156.18. MS (EI): m/z (%) = 345 (15.3) [M^+]. Anal. Calc. for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28; found: C, 69.38; H, 5.70; N, 20.07.

9-(Hex-5-enyl)-9*H*-purin-6-amine (entry **6**, Soltani Rad et al. 2009b)

Column chromatography on silica gel eluted with EtOAc afforded pure product as white solid (1.74 g, 80%); m.p. 140–141 °C. IR (KBr): 3330, 3115, 2948, 1489 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 1.31–1.40 (m, 2H, CH_2), 1.81-1.90 (m, 2H, CH_2), 2.03–2.09 (m, 2H, CH_2), 4.20 (t, J = 7.0 Hz, 2H, NCH_2), 4.93 (dd, J = 1.3, 9.2 Hz, 2H, = CH_2), 5.69–5.78 (m, 1H, = CH), 7.32 (br. s, 2H, NH_2, exchangeable with D_2O), 8.22 (s, 1H, C(2)–H of adenine), 8.25 (s, 1H, C(8)–H of adenine). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 25.18, 29.07, 32.45, 42.64, 114.85, 118.68, 138.15, 140.76, 149.48, 152.31, 155.90. MS (EI): m/z (%) = 217 (21) [M^+]. Anal. Calc. for $C_{11}H_{15}N_5$: C, 60.81; H, 6.96; N, 32.23; found: C, 60.96; H, 7.08; N, 32.35.

(E)-9-Cinnamyl-9*H*-purin-6-amine (entry **7**, Soltani Rad et al. 2009b)

Column chromatography on silica gel eluted with EtOAc afforded pure product as yellow solid (2.11 g, 84%); m.p. 237–238 °C. IR (KBr): 3355, 3130, 2950, 1492, 1453 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 4.93 (d, J = 5.0 Hz, 2H, NCH_2), 6.43 (d, J = 16.4 Hz, 1H, PhC*H*), 7.21–7.31 (complex, 6H, NCH_2C*H*, aryl), 7.37 (s, 1H, C(2)–H of adenine), 7.40 (s, 2H, NH_2, exchangeable with D_2O), 8.15 (s, 1H, C(8)–H of adenine). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 44.50, 118.63, 124.56, 126.38, 127.85, 128.57, 132.31, 135.80, 140.58, 149.35, 152.49, 155.93. MS (EI): m/z (%) = 251 (29.8) [M^+]. Anal. Calc. for $C_{14}H_{13}N_5$: C, 66.92; H, 5.21; N, 27.87; found: C, 66.81; H, 5.36; N, 27.96.

1-(6-Amino-9*H*-purin-9-yl)-3-phenoxypropan-2-ol (entry **8**, Soltani Rad et al. 2010)

Column chromatography on silica gel eluted with hexane/EtOAc (2:1) afforded pure product as white solid (2.25 g, 79%); m.p. 137–138 °C. IR (KBr): 3500, 3350, 3090, 2974, 1467, 1238 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 4.14 (dd, J = 6.2, 10.2 Hz, H, NC$H_A$$H_B$), 4.30 (dd, J = 3.7, 10.2 Hz, 1H, NC$H_A$$H_B$), 4.38–4.44 (m, 1H, C*H*OH), 4.47 (s, 1H, OH, exchangeable with D_2O), 4.60–4.65 (m, 2H, OCH_2), 7.14 (br s, 2H, NH_2, exchangeable with D_2O), 7.45–7.51 (m, 5H, aryl), 8.30 (s, 1H, C(2)–H of adenine), 8.42 (s, 1H, C(8)–H of adenine). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 46.72, 69.48, 70.07, 114.64, 119.09, 121.11, 129.85, 141.92, 150.05, 152.76, 156.32, 158.56. MS (EI): m/z (%) = 285 (14.6) [M^+]. Anal. Calc. for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55; found: C, 59.03; H, 5.21; N, 24.67.

6-Chloro-9-(4-(4-chlorophenoxy)butyl)-9*H*-purine (entry **9**)

Column chromatography on silica gel eluted with hexane/EtOAc (2:1) afforded pure product as white solid (2.73 g, 81%); m.p. 110–111 °C. IR (KBr): 3095, 2947, 2873, 1591, 1473, 1238, 1045 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 1.61–1.72 (m, 2H, NCH_2CH_2), 1.94–2.05 (m, 2H, OCH_2CH_2), 3.91 (t, J = 6.3 Hz, 2H, NCH_2), 4.34 (t, J = 7.0 Hz, 2H, OCH_2), 6.83–6.89 (complex, 3H, aryl, C(2)–H of purine), 7.21–7.27 (m, 2H, aryl), 8.69 (s, 1H, C(8)–H of purine). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 25.65, 25.78, 43.53, 67.07, 116.04, 124.07, 129.06, 130.78, 147.41, 148.91, 151.33, 151.88, 157.21. MS (EI): m/z (%) = 336 (30.8) [M^+]. Anal. Calc. for $C_{15}H_{14}Cl_2N_4O$: C, 53.43; H, 4.18; N, 16.62; found: C, 53.28; H, 4.34; N, 16.53.

7-Allyl-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (entry **10**, Soltani Rad et al. 2009b)

Column chromatography on silica gel eluted with hexane/EtOAc (1:1) afforded pure product as white solid (2.09 g, 95%); m.p. 103–104 °C. IR (KBr): 3050, 2987, 2890, 1725, 1708, 1473 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 3.17 (s, 3H, N(3)–CH_3), 3.36 (s, 3H, N(1)–CH_3), 4.73 (d, J = 5.2 Hz, 2H, NCH_2), 5.00–5.13 (dd, J = 11.5, 16.4 Hz, 2H, = CH_2), 5.77–5.93 (m, 1H, = CH), 7.40 (s, 1H, C(8)–H of theophylline). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 27.80, 29.61, 48.83, 106.71, 119.18, 132.06, 140.71, 148.64, 151.50, 154.95. MS (EI): m/z (%) = 220 (25.4) [M^+]. Anal. Calc. for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44; found: C, 54.68; H, 5.57; N, 25.32.

7-Benzyl-1, 3-dimethyl-1*H*-purine-2,6 (3*H*,7*H*)-dione (entry **11**, Soltani Rad et al. 2009b)

Column chromatography on silica gel eluted with hexane/EtOAc (1:1) afforded pure product as white solid (2.51 g, 93%); m.p. 158–159 °C. IR (KBr): 3100, 2980, 2895, 1720, 1705, 1471 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 3.31 (s, 3H, N(3)–CH_3), 3.49 (s, 3H, N(1)–CH_3), 5.42 (s, 2H, NCH_2), 7.12–7.31 (m, 5H, aryl), 7.54 (s, 1H,

C(8)–H of theophylline). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 27.92, 29.68, 50.16, 106.87, 127.37, 127.88, 128.68, 135.39, 140.89, 148.77, 151.55, 155.14. MS (EI): m/z (%) = 270 (31.4) [M^+]. Anal. Calc. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73; found: C, 62.35; H, 5.31; N, 20.61.

7-(2-Hydroxy-3-phenoxypropyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (entry **12**, Soltani Rad et al. 2010)

Column chromatography on silica gel eluted with hexane/EtOAc (2:1) afforded pure product as white solid (2.97 g, 90%); m.p. 129–130 °C. IR (KBr): 3500, 3100, 2943, 1725, 1710, 1462, 1303, 1055 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ_{ppm} = 3.37 (s, 3H, N(3)–CH_3), 3.56 (s, 3H, N(1)–CH_3), 4.07 (dd, J = 3.5, 13.4 Hz, 2H, NCH_2), 4.18 (s, 1H, OH exchangeable with D_2O), 4.41–4.51 (complex, 2H, OCH_AH_B, CHOH), 4.65 (dd, J = 2.5, 13.4 Hz, 1H, OCH_AH_B), 6.87-7.01 (m, 3H, aryl), 7.25–7.32 (m, 2H, aryl), 7.66 (s, 1H, C(8)–H of theophylline). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_{ppm} = 27.96, 29.76, 49.65, 68.68, 68.82, 106.97, 114.35, 121.36, 129.49, 142.66, 148.75, 151.29, 155.59, 158.04. MS (EI): m/z (%) = 330 (19.2) [M^+]. Anal. Calc. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96; found: C, 58.29; H, 5.36; N, 17.08.

Butyl 3-(1*H*-benzo[d]imidazol-1-yl)propanoate (entry **13**, Soltani Rad et al. 2010)

Column chromatography on silica gel eluted with hexane/EtOAc (2:1) afforded pure product as white solid (2.27 g, 92%); m.p. 114–115 °C. IR (KBr): 3088, 2960, 1735, 1493, 1245 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ_{ppm} = 0.73 (t, J = 7.3 Hz, 3H, CH_3), 1.09–1.23 (m, 2H, CH_3CH_2), 1.35–1.47 (m, 2H, OCH_2CH_2), 2.69 (t, J = 6.7 Hz, 2H, O = CCH_2), 3.90 (t, J = 6.7 Hz, 2H, NCH_2), 4.30 (t, J = 6.5 Hz, 2H, OCH_2), 7.13–7.29 (m, 2H, aryl), 7.67–7.71 (m, 2H, aryl), 7.84 (s, 1H, C(2)–H of benzimidazole). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_{ppm} = 13.55, 18.91, 30.36, 34.30, 40.26, 64.93, 109.32, 120.33, 122.11, 122.92, 133.32, 143.31, 143.73, 170.64. MS (EI): m/z (%) = 246 (17.8) [M^+]. Anal. Calc. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37; found: C, 68.42; H, 7.48; N, 11.26.

2-(1*H*-Benzo[*d*]imidazol-1-yl)acetonitrile (entry **14**, Soltani Rad et al. 2010)

Column chromatography on silica gel eluted with hexane/EtOAc (2:1) afforded pure product as white solid (1.43 g, 91%); m.p. 58–59 °C. IR (KBr): 3090, 2984, 2837, 2200, 1450 cm^{-1}. ^{1}H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 5.69 (s, 2H, NCH_2), 7.18–7.39 (m, 2H, aryl), 7.61-7.78 (m, 2H, aryl), 8.37 (s, 1H, C(2)–H of benzimidazole). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 46.77, 111.17, 116.14, 119.47, 121.84, 122.06, 122.40, 129.12, 143.99. MS (EI): m/z (%) = 157 (12.7) [M^+]. Anal. Calc. for $C_9H_7N_3$: C, 68.78; H, 4.49; N, 26.74; found: C, 68.64; H, 4.59; N, 26.83.

1-(3-(Naphthalen-2-yloxy)propyl)-1*H*-imidazole (entry **15**, Soltani Rad et al. 2009b)

Column chromatography on silica gel eluted with EtOAc afforded pure product as white solid (2.37 g, 94%); m.p. 99–100 °C. IR (KBr): 3150, 2948, 2887, 1462 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ_{ppm} = 2.15–2.25 (m, 2H, CH_2), 3.93 (t, J = 5.6 Hz, 2H, NCH_2), 4.11 (t, J = 5.6 Hz, 2H, OCH_2), 6.89 (s, 1H, C(5)–H of imidazole), 7.06 (s, 1H, C(4)–H of imidazole), 7.12–7.15 (m, 2H, aryl), 7.30–7.40 (m, 2H, aryl), 7.46 (s, 1H, C(2)–H of imidazole), 7.68 (s, 1H, aryl), 7.72–7.76 (m, 2H, aryl). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_{ppm} = 30.71, 43.45, 63.74, 106.74, 118.59, 119.02, 123.84, 126.51, 126.77, 127.66, 129.10, 129.57, 129.63, 134.46, 137.31, 156.37. MS (EI): m/z (%) = 252 (21.6) [M^+]. Anal. Calc. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10; found: C, 76.07; H, 6.50; N, 11.25.

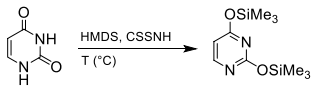
Results and discussion

To optimize the reaction condition, the silylation of uracil with HMDS in the presence of CSSNH was investigated as a sample reaction. To this end, the effect of temperature and the amount of catalyst was studied on the silylation of uracil.

Since the reaction temperature has a significant role on the reaction progress, the impact of temperature variations was investigated on sample reaction (Table 1). As shown in Table 1, the reaction was not achieved at room temperature even after 120 min (entry 1). When the reaction time was prolonged up to 720 min at R.T., a trace amount of silylated uracil was obtained (entry 2). The data in Table 1 demonstrate that elevation in temperature resulted in enhancement of reaction efficiency. The silylated uracil was quantitatively obtained when the reaction was performed at 90 °C (Table 1, entry 6). However, no more improvement in terms of reaction time and yield was obtained by the increment of temperature from 90 °C up to reflux condition (Table 1, entries 6–9). Therefore, all silylation reactions of nucleobases were carried out 90 °C. It is also worth mentioning that the previous methods used for silylation of nucleobases were conducted in refluxing HMDS.

In another experiment, different amounts of loaded catalyst were studied to obtain an efficient progress of sample reaction (Table 2). As can be seen in Table 2, the amount of CSSNH plays a significant role in upgrading of the silylation reaction of uracil. Practically, it was found that the silylation of uracil in the absence of catalyst acquires low yield of silylated adduct in a long reaction time.

Table 1 Effect of temperature variation on silylation of uracil



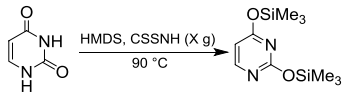
Entry	Temperature (°C)	Time (min)	Yield[a] (%)
1	r.t.	120	NR[b]
2	r.t.	720	Trace
3	40	120	14
4	60	75	32
5	80	40	61
6	90	22	100
7	100	22	100
8	110	22	100
9	Reflux	20	100

Reaction conditions: uracil (1 mmol), HMDS (10 mL), and CSSNH (0.05 g)

[a]GC yield

[b]No reaction

Table 2 Effect of loaded catalyst on silylation of uracil



Entry	×g CSSNH	Time (min)	Yield[a] (%)
1	–	420	12
2	0.02	60	64
3	0.03	50	76
4	0.04	35	89
5	0.05	22	100
6	0.06	22	100
7	0.07	21	100

Reaction conditions: uracil (1 mmol) and HMDS (10 mL)CSSNH (×g)

[a]GC yield

As shown in Table 2, the increase in loading of catalyst up to 0.05 g enhances the reaction yield and accelerates the reaction rate (entries 2–5). The best result was obtained when the silylation of uracil was achieved in the presence of 0.05 g CSSNH at 90 °C (Table 2, entry 5). Additionally, loading more catalyst from 0.05 up to 0.07 had no considerable effect on the progress of sample reaction (Table 2, entries 5–7).

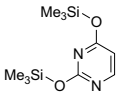
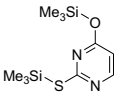
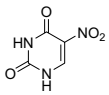
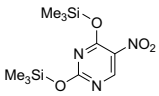
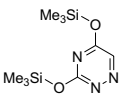
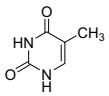
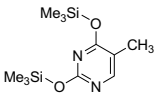
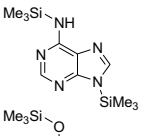
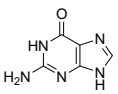
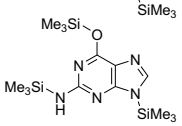
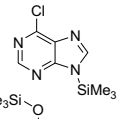
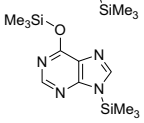
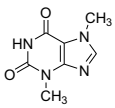
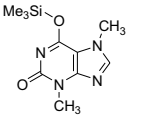
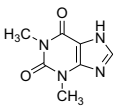
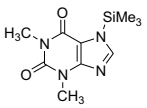
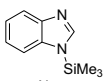
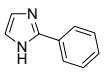
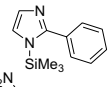
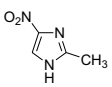
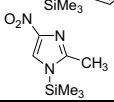
With optimized reaction conditions in hand, we then screened the scope, versatility, and general applicability of the present protocol in trimethylsilylation of structurally diverse purine and pyrimidine nucleobases as well as other N-heterocycles (Table 3). As can be seen in Table 3, all examined substrates efficiently undergo the silylation reaction in the presence of CSSNH using HMDS at 90 °C to afford their corresponding trimethylsilyl derivatives in almost quantitative yields. Practically, CSSNH is a highly efficient heterogeneous nanocatalyst for trimethylsilylation of pyrimidine and purine nucleobases as well as their related analogues (Table 3, entries 1–11). Although guanine is known as the most insoluble and unreactive purine nucleobase; however, trimethylsilylation of guanine was competently achieved using the current protocol (Table 3, entry 7). Furthermore, the other examined *N*-heterocycles including benzimidazole, imidazole, 2-phenyl imidazole, and 2-methyl-4-nitro-1*H*-imidazole were completely converted to their corresponding trimethylsilyl derivatives (Table 3, entries 12–15).

We also compared the potency of CSSNH with that of SSA as the only reported heterogeneous catalyst for silylation of nucleobases and other *N*-heterocycles (Soltani Rad et al. 2010). The results in Table 3 clearly indicate that there are no distinguishable differences between the potency of CSSNH and SSA in the case of pyrimidine nucleobases (entries 1, 3–5) and some azole derivatives (entries 12–14). However, when the CSSNH is used for silylation of 2-thiouracil and 2-methyl-4(5)-nitroimidazole, the corresponding silylated derivatives were obtained in shorter reaction times compared to SSA (entries 2 and 15, respectively). More satisfactory results were obtained in the case of purine nucleobases and their analogues when CSSNH was employed as the catalyst (entries 6–11). It is also worthy to mention that CSSNH unlike SSA has a very mild acidic character and consequently its application has a preference compared to SSA especially in the case of acid-sensitive substrates. The acid content of CSSNH was also measured by a simple titration using standard NaOH solution. The titration result has clearly indicated that each 0.05 g of CSSNH contains 0.04 mmol of H^+ whereas the same titration for 0.05 g of SSA resulted in 0.13 mmol of H^+ (Shaterian et al. 2008; Shah et al. 2014).

To evaluate the efficiency and catalytic potency of CSSNH, the trimethylsilylation of uracil, adenine, and benzimidazole was achieved using CSSNH, TMSCl, and $(NH_4)_2SO_4$ under the optimized condition. The comparative results are depicted in Table 4. As shown in Table 4, TMSCl and $(NH_4)_2SO_4$ are less efficient than CSSNH for silylation of nucleobases especially in the case of reaction times.

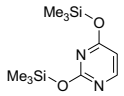
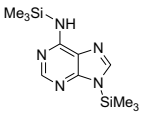
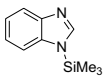
To prove the recyclability and heterogeneous nature of CSSNH, after completion of the sample reaction, the catalyst was filtered using a sintered glass funnel and washed twice with hot THF (2×3 mL). After recovering and drying the catalyst, CSSNH was directly employed for silylation of uracil in the next run while the fresh CSSNH was not added

Table 3 Silylation of nucleobases and other *N*-heterocycles with HMDS using CSSNH and SSA catalysts

Entry	Substrate	Product	CSSNH	SSA
			Time (min.)/Yield [a] (%)	Time (min.)/Yield [a] (%)
1			22/100	30/100
2			85/100	120/100
3			22/100	30/100
4			22/100	30/100
5			24/100	35/100
6			150/100	180/199
7			1200/91	1440/90
8			55/100	80/100
9			70/100	90/100
10			85/100	120/100
11			40/100	60/100
12			20/100	30/100
13			7/100	9.6/100
14			20/100	30/100
15			90/100	120/100

Reaction conditions: nucleobase (1 mmol), HMDS (10 mL), CSSNH (0.05 g), 90 °C. [a] GC yield.

Table 4 The comparative results for silylation of nucleobases and other *N*-heterocycles using HMDS in the presence of CSSNH, TMSCl, and $(NH_4)_2SO_4$

Entry	Substrate	Product	Time (min.)/ Yield [a] (%)		
			CSSNH	TMSCl	$(NH_4)_2SO_4$
1			22/100	210/100	120/100
2			150/100	970/78	650/86
3			20/100	60/100	50/100

[a] GC yield.

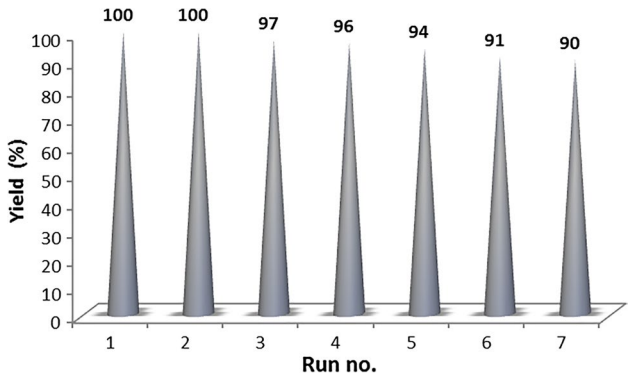


Fig. 2 The reusability of CSSNH for silylation of uracil

to the reaction flask. The reusability of catalyst was evaluated for seven runs (Fig. 2). As shown in Fig. 2, CSSNH is an efficient recyclable and reusable heterogeneous catalyst with negligible decline in its reactivity (Molnár and Papp 2017). To determine the catalyst stability, the IR spectrum of recycled catalyst after seven sequential runs was taken and compared with that of the fresh catalyst (Fig. 3). As can be seen in Fig. 3, no noticeable alteration or change in structure and functionalities of CSSNH is observed and this can be attributed to stability of catalyst.

To evaluate the feasibility of the present protocol on a large-scale synthesis, the trimethylsilylation of uracil was achieved on a 200-mmol scale using the optimized reaction conditions. Interestingly, the corresponding trimethylsilyl uracil was obtained almost in a quantitative yield after 35 min.

In the next step of this approach, the obtained presilylated nucleobases and other *N*-heterocycles underwent the reaction with different alkyl halides, butyl acrylate as a Michael acceptor, and 2-(phenoxymethyl)oxirane as an epoxide. To this end, tetra-*n*-butylammonium fluoride (TBAF) was applied as a desilylating reagent (Scheme 1). The structures of synthesized acyclic nucleosides are depicted in Table 5. As shown in Table 5, the corresponding *N*-alkylated products were obtained in good-to-excellent yields.

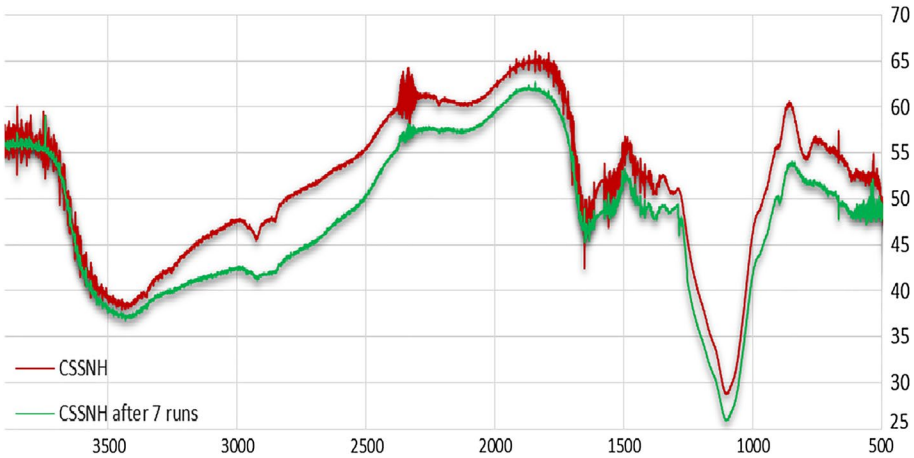
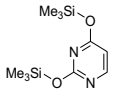
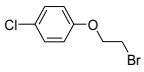
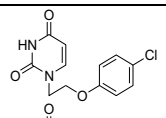
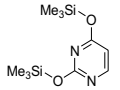
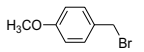
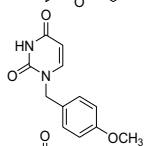
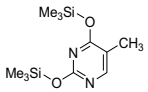
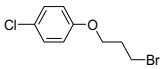
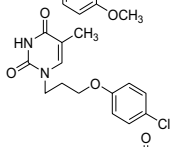
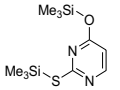
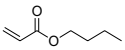
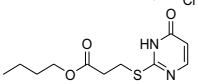
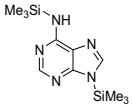
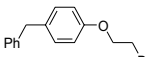
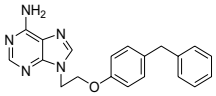
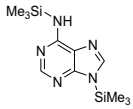
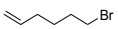
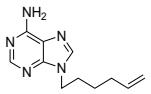
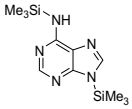
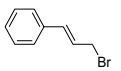
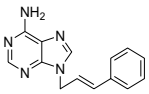
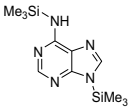
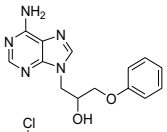
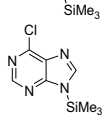
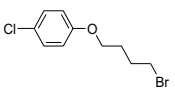
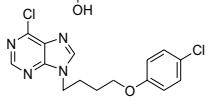
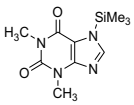
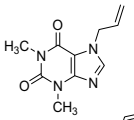
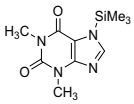
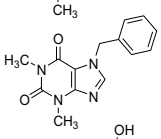
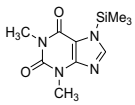
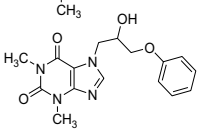
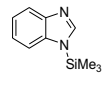
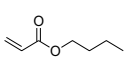
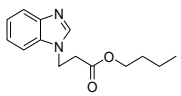
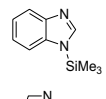


Fig. 3 Comparison between IR spectrum of fresh CSSNH and recovered CSSNH after seven sequential runs

Table 5 The synthesized *N*-alkyl nucleobases and other related *N*-heterocycles

Entry	Substrate	Electrophile	Product [a]	Yield [b] (%)
1				86
2				90
3				87
4				85
5				82
6				80
7				84
8				79
9				81
10				95
11				93
12				90
13				92
14				91
15				94

[a] All products were characterized by ^{1}H and ^{13}C NMR, IR, CHN, and MS analysis. [b] Isolated yield.

Conclusions

In summary, a rapid, simple and highly efficient protocol for silylation of structurally diverse nucleobases and other related *N*-heterocycles using CSSNH as a green heterogeneous hybrid nanocatalyst is described. The efficiency of CSSNH for silylation of nucleobases was proved by convenient *N*-alkylation of the presilylated substrates with different carbon electrophiles. CSSNH affords remarkable advantages such as recoverability and reusability for at least seven reaction runs, eco-friendly nature, ease of preparation and handling, cheapness, and feasibility of application in large-scale synthesis. In addition, CSSNH proved to be a more efficient catalyst in comparison with SSA, TMSCl, and $(NH_4)_2SO_4$ for silylation of purine nucleobases and their analogues.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Affiliations

Somayeh Behrouz[1] · Mohammad Navid Soltani Rad[1] · Mohammad Amin Piltan[1]

[1] Medicinal Chemistry Research Laboratory, Department of Chemistry, Shiraz University of Technology, Shiraz 71555-313, Iran