ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 9269–9271

www.rsc.org/chemcomm

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Rhodium acetate/base-catalyzed N-silylation of indole derivatives with hydrosilanes†

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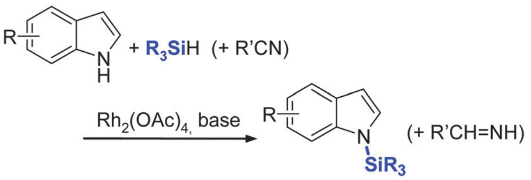
Received 19th June 2012, Accepted 26th July 2012
DOI: 10.1039/c2cc34381a

In the presence of $Rh_2(OAc)_4$ (OAc = acetate) and TBA_2WO_4 (TBA = tetra-*n*-butylammonium), the N-silylation of indole derivatives with hydrosilanes efficiently proceeded to give the corresponding N-silylated indoles in high yields. Pyrrole and carbazole were also N-silylated with the combined catalysts.

Heteroarenes have been utilized as intermediates in a wide range of organic syntheses,[1] and they are essentially pharmacophores.[2] In particular, much attention has been paid to the development of efficient procedures for synthesis and functionalization of indoles[3] because the indole rings are some of the most important skeletons ubiquitously found in many natural products and biologically active compounds.[4] N-Silylated indoles have been recognized as very important synthons and widely utilized for synthesis of indole-based natural products and drug candidates.[5] In addition, Hartwig and co-workers have recently reported the site-selective borylation of indoles using *in situ* generated N-silylated indoles as synthetic intermediates.[6] Up to the present, the vast majority have generally utilized activated indoles and halosilanes for synthesis of silylated indoles; for example, N-silylation has been performed by activation (deprotonation) of indoles, followed by coupling with chlorosilanes.[7] However, this antiquated N-silylation requires stoichiometric reagents such as alkyl lithium and sodium hydride for pre-activation of indoles, and at least equimolar amounts of by-products are formed during not only the N-silylation but also the pre-activation of indoles. Thus, the development of efficient procedures instead of the above-mentioned antiquated silylations, *i.e.*, the direct use of indoles without pre-activation using stoichiometric reagents and the replacement of halosilanes with hydrosilanes or their surrogates, is an important subject in modern organic synthesis.

Hydrosilanes are readily available, easy-to-handle, nontoxic, and inexpensive silylating reagents.[8] Therefore, catalytic direct cross-coupling of indoles with hydrosilanes is the most attractive alternative for the synthesis of silylated indoles. To date, several procedures for the catalytic synthesis of silylated indoles with hydrosilanes have been reported.[9–11] Lu and Falck[9] reported the Ir(I)-catalyzed C2-silylation of indoles with hydrosilanes. Tatsumi and co-workers[10] reported the Ru(II)-catalyzed C3-silylation of N-protected indoles with hydrosilanes. To date there have been only a few reports on the N-silylation of indoles with hydrosilanes,[6,11]‡ as far as we know, due to their strong N–H bonds in comparison with common amines.[12] Herein, we demonstrate the N-silylation of indoles with hydrosilanes using simple $Rh_2(OAc)_4$ and O-donor bases, especially TBA_2WO_4 [eqn (1)].[13]



(1)

Initially, the N-silylation of indole (**1a**) with dimethylphenylsilane (**2a**, five equivalents with respect to **1a**) was carried out in the presence of catalytic amounts of various metal salts and complexes (*e.g.*, Rh, Pd, Ru, Pt, Ir, Cu, Ag, Au, Co, Ni, and Zn, 2 mol% with respect to **1a**) and TBA_2WO_4 (2 mol% with respect to **1a**) (Table S1, ESI†). No reaction proceeded in the absence of metal catalysts and/or bases. Among the metal catalysts examined, only $Rh_2(OAc)_4$ gave the corresponding N-silylated indole in a high yield; for example, when the silylation was carried out with $Rh_2(OAc)_4$ (1 mol% with respect to **1a**) and TBA_2WO_4 (2 mol% with respect to **1a**) at 50 °C for 2 h, the corresponding N-silylated indole (**3aa**) was obtained in >99% yield (Table 1, entry 1). In this case, no C2- and C3-silylated indoles were produced. Notably, the N-silylation of **1a** efficiently proceeded even with two equivalents of **2a**, affording **3aa** in 83% yield. $Rh_2(pfb)_4$ (pfb = perfluorobutyrate, analogue of $Rh_2(OAc)_4$) also gave **3aa** in a moderate yield (Table S2, ESI†). Other rhodium complexes such as $[RhCl_2Cp^*]_2$ (Cp* = pentamethylcyclopentadienyl), $[Rh(cod)Cl]_2$ (cod = 1,5-cyclooctadiene), and $Rh(PPh_3)_3Cl$ were not effective (Table S2, ESI†), while these complexes have been reported to be active for dehydrosilylation of alcohols[14] and hydrosilylation of alkenes and alkynes.[15]

Kinds of bases were also crucial for the N-silylation of **1a**. Among the bases examined, TBA_2WO_4 was the most suitable for the N-silylation of **1a** (Table S3, ESI†). Other O-donor

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† Electronic supplementary information (ESI) available: Experimental details, data of N-silylated products, and Tables S1–S4, Fig. S1–S3, and Scheme S1. See DOI: 10.1039/c2cc34381a

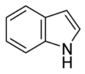
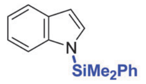
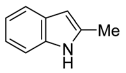
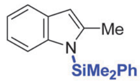
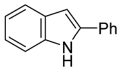
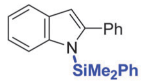
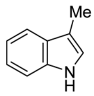
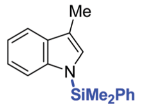
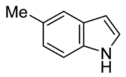
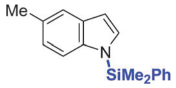
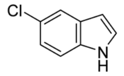
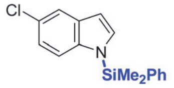
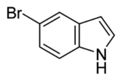
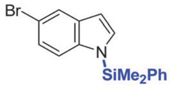
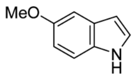
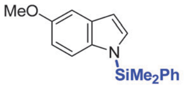
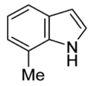
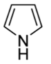
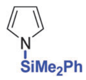
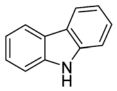
Table 1 N-silylation of **1a** with various hydrosilanes[a]

1a **3aa–3ae**

Entry	Hydrosilane	Temp./°C	Time/h	Conv. (%)	Yield (%)
1	$PhMe_2Si$–H (**2a**)	50	2	> 99	> 99 (77)
2[b]	Ph_2MeSi–H (**2b**)	80	3	95	79
3[b]	Ph_3Si–H (**2c**)	80	24	63	46
4[c]	Et_3Si–H (**2d**)	80	12	87	85 (76)
5[b,c]	*t*-$BuMe_2Si$–H (**2e**)	80	24	66	66
6	*i*-Pr_3Si–H (**2f**)	80	24	1	Nd

[a] Reaction conditions: $Rh_2(OAc)_4$ (1 mol% with respect to **1a**), TBA_2WO_4 (2 mol% with respect to **1a**), **1a** (0.5 mmol), hydrosilane (2.5 mmol), CH_3CN (2 mL), Ar (1 atm). Conversions and yields are based on **1a** and determined by GC analysis. Values in the parentheses are the yields of isolated products. Nd = not detected. [b] $Rh_2(OAc)_4$ (2 mol% with respect to **1a**), TBA_2WO_4 (4 mol% with respect to **1a**). [c] CH_3CN (1 mL).

Table 2 N-silylation of various heterocycles with **2a**[a]

Entry	Substrate		Time/h	Silylated product		Yield (%)
1		**1a**	2		**3aa**	> 99 (79)
2		**1b**	4		**3ba**	92
3[b]		**1c**	4		**3ca**	73 (78)
4		**1d**	2		**3da**	97 (88)
5		**1e**	2		**3ea**	99 (76)
6		**1f**	4		**3fa**	> 99
7		**1g**	4		**3ga**	82 (55)
8		**1h**	2		**3ha**	> 99
9		**1i**	4		**3ia**	88 (78)
10		**4a**	2		**5aa**	98 (74)
11[c]		**6a**	6		**7aa**	98

[a] Reaction conditions: $Rh_2(OAc)_4$ (1 mol% with respect to nitrogen heterocycles), TBA_2WO_4 (2 mol% with respect to nitrogen heterocycles), nitrogen heterocycles (0.5 mmol), **2a** (2.5 mmol), CH_3CN (2 mL), Ar (1 atm), 50 °C. Yields are based on nitrogen heterocycles and determined by GC analysis. Values in the parentheses are the yields of isolated products. [b] $Rh_2(OAc)_4$ (2 mol% with respect to nitrogen heterocycles), TBA_2WO_4 (4 mol% with respect to nitrogen heterocycles). [c] 80 °C.

bases such as KO*t*-Bu, K_2CO_3, TBAOH, K_3PO_4, and Cs_2CO_3 also gave **3aa** in moderate to high yields, while N-donor bases such as triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were not effective (Table S3, ESI†). The selection of solvents was also very important; the reaction efficiently proceeded in acetonitrile and benzonitrile, while the reaction hardly proceeded using other solvents such as DMSO, DMF, and acetone (Table S4, ESI†). Not only **2a** but also various structurally diverse hydrosilanes could be utilized as silylating reagents. The N-silylation with diphenylmethylsilane (**2b**), triphenylsilane (**2c**), triethylsilane (**2d**), and *tert*-butyldimethylsilane (**2e**) afforded the corresponding N-silylated indoles in moderate to high yields (Table 1, entries 2–5). On the other hand, the reaction with triisopropylsilane (**2f**) hardly proceeded likely due to the steric hindrance of the isopropyl groups (Table 1, entry 6).

Next, the N-silylation of various indoles with **2a** was carried out (Table 2). Methyl substitutions at C3 and C5 positions of indole rings did not affect the reaction rates (Table 2, entries 4 and 5), while substitutions at C2 and C7 positions required longer reaction times due to the steric effect of the methyl groups (Table 2, entries 2 and 9). Similarly, the N-silylation of 2-phenylindole (**1c**) required a longer reaction time and a large amount of $Rh_2(OAc)_4$ and TBA_2WO_4 to attain a high yield of the corresponding N-silylated indole (Table 2, entry 3). The N-silylation of indoles with electron-donating as well as electron-withdrawing substituents at C5 positions efficiently proceeded to give the corresponding substituted N-silylated indoles in high yields ($\geq$ 82% yields) (Table 2, entries 5–8). In the case of halo-substituted indoles, the desired N-silylated indoles were obtained without dehalogenation. Thus, it would be possible to utilize these halo-functionalities for further modification of the indole molecules.[5,11] Besides indole derivatives, pyrrole (**4a**) and carbazole (**6a**) were also silylated to afford the corresponding N-silylated products in $\geq$ 98% yields (Table 2, entries 10 and 11).

The positive-ion cold-spray ionization mass (CSI-MS) spectrum of an acetonitrile solution of TBA_2WO_4 showed a set of signals due to $[TBA_3WO_4]^+$ (Fig. S1a, ESI†). Upon the addition of $Rh_2(OAc)_4$ and **2a** ($Rh_2(OAc)_4 : TBA_2WO_4 :$ **2a** = 1 : 1 : 40) to the TBA_2WO_4 solution, a new set of signals appeared, which agrees with the pattern calculated for $[TBA_2(PhMe_2Si)WO_4(PhMe_2SiOAc)]^+$ (Fig. S1b, ESI†). The new set of signals did not appear in the absence of $Rh_2(OAc)_4$. In addition, the ^1H NMR spectrum of $Rh_2(OAc)_4$ (25 mM) and **2a** (10 mM) in acetonitrile-d_3 showed signals due to dimethylphenylsilanol and H_2 (Fig. S2, ESI†), suggesting that $Rh_2(OAc)_4$ can activate **2a**. Dimethylphenylsilanol and H_2 are probably produced through the activation of **2a** by $Rh_2(OAc)_4$,§ followed by the reaction with water (including in $Rh_2(OAc)_4$ and/or the solvent). Thus, the Si–H bond of **2a** is initially activated by $Rh_2(OAc)_4$

(step 1 in Scheme S1, ESI†), and then a silicon electrophile stabilized on TBA_2WO_4 is possibly formed (step 2 in Scheme S1, ESI†). In the dehydrosilylation of alcohols with hydrosilanes using $Rh_2(pfb)_4$ (analogue of $Rh_2(OAc)_4$), the reaction mechanism of the coordination (not oxidative addition) of Si–H bonds to the Rh sites for backside nucleophilic attack by alcohols has been proposed.[16] In addition, it has been reported that a silicon electrophile can be stabilized on polyoxotungstates.[17]

The ^1H NMR spectrum of **1a** in acetonitrile-d_3 showed the signal of the NH proton at 9.4 ppm (Fig. S3a, ESI†). A significant downfield shift (from 9.4 ppm to 13.6 ppm) was observed upon addition of one equivalent of TBA_2WO_4 with respect to **1a** (Fig. S3b, ESI†). These results indicate the hydrogen-bonding interaction between TBA_2WO_4 and **1a** that could weaken the N–H bond of **1a** and facilitate the electrophilic attack of activated hydrosilanes on the nitrogen atom of **1a**. In contrast, significant downfield shifts of the NH proton of **1a** were not observed with N-donor bases such as triethylamine and DBU. Thus, these bases were not effective for the present $Rh_2(OAc)_4$-catalyzed N-silylation, as mentioned above (Table S3, ESI†).

Therefore, both activated hydrosilanes and indoles likely co-existed on the TBA_2WO_4 molecules, resulting in efficient promotion of the present N-silylation (step 3 in Scheme S1, ESI†). Acetonitrile (solvent) also takes part in the catalytic cycle; rhodium species and bases are regenerated by the hydrogenation of acetonitrile (step 4 in Scheme S1, ESI†),¶ and the catalytic cycle is complete. The present $Rh_2(OAc)_4$/base-catalyzed N-silylation of indoles with hydrosilanes likely proceeds *via* the ionic silylation mechanism shown in Scheme S1 (ESI†). In the hydrosilylation of ketones, a similar ionic hydrosilylation mechanism has been proposed.[18]

This work was supported in part by Grants-in-Aid for Scientific Researches from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Notes and references

‡ During the review process of this manuscript, Tsuchimoto and co-workers have reported the efficient zinc-catalyzed N-silylation of indoles with hydrosilanes in the presence of nitrogen bases.[11]

§ In the CSI-MS as well as ^1H and ^{29}Si NMR spectra of $Rh_2(OAc)_4$ (25 mM) and **2a** (10 mM) in acetonitrile, no signals due to the corresponding silyl metal hydride species were detected. $Rh(PPh_3)_3Cl$ and $[RuCl_2(p\text{-cymene})]_2$, which are well known to form silyl metal hydride species by oxidative addition of hydrosilanes,[14] were not effective for the N-silylation. Thus, the oxidative addition mechanism can likely be excluded for the present N-silylation.

¶ During the present N-silylation, dimethylphenylsilylethylamine formed as a co-product in all cases, which likely formed through the hydrogenation of acetonitrile followed by hydrosilylation. For example, dimethylphenylsilylethylamine formed in 95% yield (based on **1a**) during the N-silylation of **1a** with **2a** under the conditions described in Table 2. Although silylamines formed from nitriles (solvents) as co-products during the present N-silylation of indoles, silylamines can be further converted into the corresponding primary amines by simple hydrolysis.

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