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Tris(trimethylsilyl)silane in the Alkylation of Heteroaromatic Bases with Alkyl Halides

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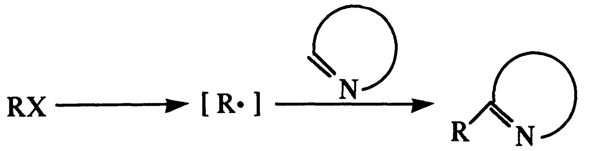
Protonated heteroaromatic bases were easily alkylated via radical pathways using alkyl halides in the presence of tris(trimethylsilyl)silane under photochemical or thermal conditions.

The substitution of heteroaromatic bases by nucleophilic carbon-centered radicals is very important and interesting because the reaction shows the opposite reactivity and selectivity to ionic substitution like the Friedel-Crafts reactions. Hitherto the radical reactions onto heteroaromatic bases have been well studied.[1-4] However, most of them have been carried out under oxidative conditions as shown below (I in Scheme 1).[1,2] To our knowledge, only two methods are known for the alkylation of heteroaromatic bases under non-oxidative conditions (II in Scheme 1),[3,4] where the starting material is the carboxylic acid or mono alkyl ester of oxalic acids.



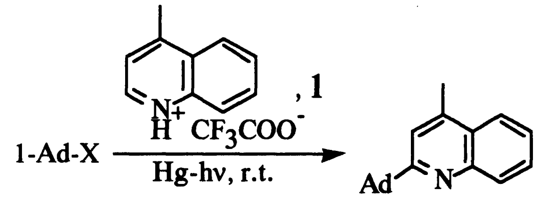
I) Oxidative conditions
(X = I, COOH, OOC-COOH)
i) Peroxide/Fe^{2+}, Ti^{3+}, Ag^{+}, Mn^{3+}, etc.[1)]
ii) Trivalent iodine compounds[2)]

II) Non-oxidative conditions
(X = COOH, OOC-COOH)
i) Ester of N-hydroxy-2-thiopyridone[3)]
ii) Ester of benzophenone oxime[4)]

Scheme 1.

As a part of our study on the radical alkylation of aromatic compounds with various alkyl derivatives under non-oxidative conditions, we report the radical alkylation of heteroaromatic bases with alkyl halides by utilizing tris(trimethylsilyl)silane which is a reductive, non-toxic and simple reagent.[5)] Although this silane compound was recently reported as a valuable reagent for radical-mediated organic synthesis, i.e. reduction and

Table 1. Relative Reactivities with Non-Oxidative Reagents[a)]

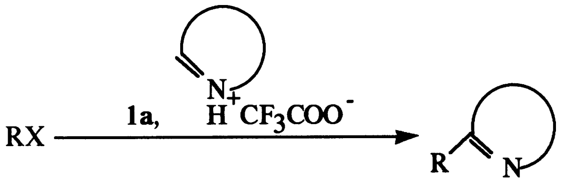


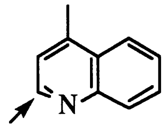
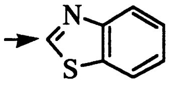
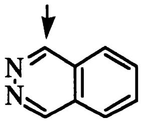
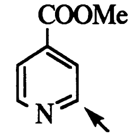
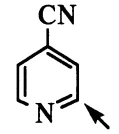
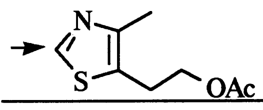
1 Reagent[b)]		Yield/%	
		1-Ad-I	1-Ad-Br
$(Me_3Si)_3SiH$	(1a)	89	73
$(Me_3Si)_3SiH$-AIBN	(1a-AIBN)	87	61
$(Me_3Si)_4Si$	(1b)	88	83
$(Me_3Si)_2$	(1c)	17	2
$(Bu_3Sn)_2$	(1d)	74	16
Bu_3SnH-AIBN	(1e-AIBN)	51	9
Ph_2SiH_2-AIBN	(1f-AIBN)	10	4

a) Hg-hv: High-pressure mercury lamp
b) Based on alkyl halide, 2.0 equiv. of 1 was used.

carbon-carbon bond forming reactions,5) it has never been used as radical alkylation reagent onto heteroaromatic bases with alkyl halides. In our previous study on the photochemical reactivity of tetrakis(trimethylsilyl)silane-mediated alkylation of heteroaromatic bases,6) we carried out the alkylation of lepidine with adamantyl halides in the presence of tetrakis(trimethylsilyl)silane7) under irradiation with high-pressure mercury lamp and the corresponding adamantylated lepidine was obtained in good yield. During the study, we thought that tris(trimethylsilyl)silyl halide or tris(trimethylsilyl)silane should be formed as a byproduct. However, tris(trimethylsilyl)silyl halide was not observed and only a trace amount of tris(trimethylsilyl)silane was observed during the reaction. Thus, we presumed that these formed polysilane species might further react with alkyl halides as radical initiators again. In practice, tris(trimethylsilyl)silane **1a**8) reacted with alkyl halides in the presence of protonated heteroaromatic bases to give the corresponding alkylated lepidine under the same irradiation conditions as shown in Table 1. For example, alkylation of the protonated lepidine with adamantyl iodide and adamantyl bromide in the presence of **1a** (2.0 equiv.) under photochemical conditions gave 2-adamantyl-4-methylquinoline in 89% and 73% yields, respectively. This fact is very surprising because tris(trimethylsilyl)silane is a reducing agent like tributyltin hydride.5) Namely, tris(trimethylsilyl)silane behaves like an oxidizing agent in this substitution reaction. Further, under the thermal conditions with **1a** (2.0 equiv.) and AIBN (2.0 equiv.), the same alkylated compound was also obtained in good yield, although the same reaction with

Table 2. Alkylation of Heteroaromatic Bases



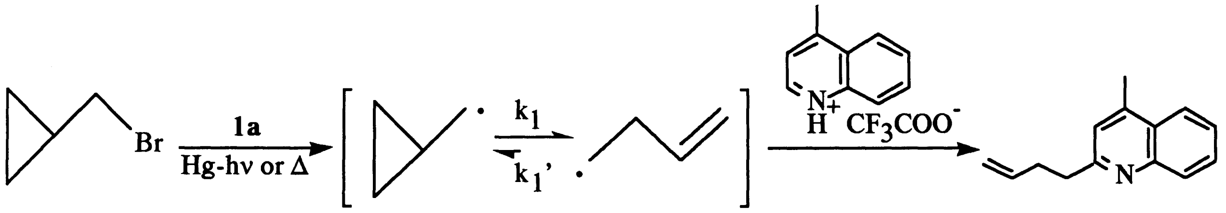
Base[a]	RX	Yield / %	
		Δ[b]	hν[c]
	1-AdI	86	89
	1-AdBr	90	73
	c-$C_6H_{11}I$	76	76
	c-$C_6H_{11}Br$	79	44
	n-$C_8H_{17}I$	44	63
	n-$C_8H_{17}Br$	43	33
	t-BuBr	81	75
	Menthyl Bromide	30	56
	Cholestanyl Bromide	59	58
	1-AdBr	83	35
	Cholestanyl Bromide	20	35
	1-AdBr	55	17
	1-AdBr	62	35
	1-AdBr	57	26
	1-AdBr	45	30

a) → : C-C Bond forming position.

b) Δ : Refluxing in benzene in the presence of AIBN.

c) hν : Irradiation with high-pressure mercury lamp in CH_2Cl_2.

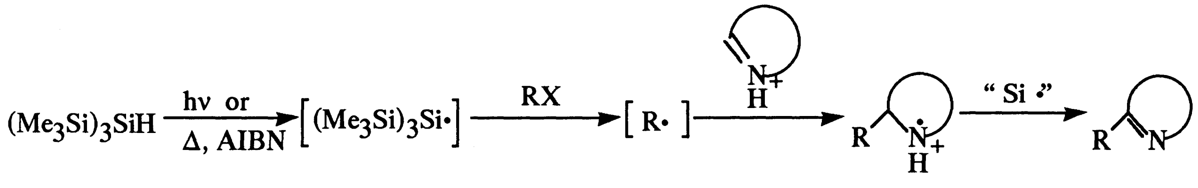
tetrakis(trimethylsilyl)silane and AIBN did not work at all. The results with other heteroaromatic bases and alkyl halides are summarized in Table 2 and suggest that **1a**, which has been thought as a reducing agent like tributyltin hydride, play a role as a non-reductive reagent like tetrakis(trimethylsilyl)silane. However, other silane compounds, i.e., hexamethyl disilane **1c** and diphenylsilane **1f**, did not act as effective reagents for alkylation. Hexabutylditin is an efficient alkylation reagent only with alkyl iodides among **1c**, **1d**, **1e**, and **1f**. However, it is well known that organotin compounds are toxic. The reason why the alkylation of heteroaromatic bases with **1a** proceeds effectively under both thermal and photochemical conditions, is that the rates of the alkylation onto lepidine by the alkyl radical and the reduction of the alkyl radical by tris(trimethylsilyl)silane are nearly same order.[9] Therefore the alkylated products could be obtained in good yields with tris(trimethylsilyl)silane in the presence of excess lepidine. Similarly under the thermal conditions with **1a**, the alkylation of heteroaromatic bases has been achieved effectively in the presence of excess AIBN (2.0 equiv.) to produce tris(trimethylsilyl)silyl radical, which abstracts halogen atoms of alkyl halides to generate the corresponding alkyl radicals. However, alkyl chloride did not react with heteroaromatic bases with **1a** because abstraction of the chlorine atom in alkyl chloride by the silyl radical species does not occur smoothly. In the reaction with cyclopropylmethyl bromide with **1a** (Scheme 2), only the ring-opened compound was obtained. This could be explained as follows; the cyclopropylmethyl radical formed underwent rapid ring-opening[10] followed by trapping of the formed 3-butenyl radical by protonated lepidine to give 2-(3-butenyl)-4-methylquinoline as a sole product as shown below. Based on these results, the alkylation of heteroaromatic bases with alkyl halides in the presence of **1a** may proceed via the formation of tris(trimethylsilyl)silyl radical, then halogen atom abstraction by the silyl radical to give the corresponding alkyl radical which further reacts with protonated heteroaromatic bases to give the alkylated heteroaromatic bases, via the oxidation of aminium radical intermediate by silyl radical species. Studies on the detailed reaction mechanism and further applications are underway in this laboratory.



$k_1 = 1.3 \times 10^8\ s^{-1}$
$k_1' = 1.0 \times 10^4\ s^{-1}$ (25 °C)[10]

hν : 55%
Δ : 58%

Scheme 2.



" Si •" (hydrogen abstraction species) : (Me$_3$Si)$_3$Si•, (Me$_3$Si)$_2$HSi•, etc.

Scheme 3.

The typical experimental procedure is as follows: To a mixture of adamantyl bromide (0.5 mmol) and lepidinium salt (2.5 mmol) in benzene (6 ml) were added tris(trimethylsilyl)silane (1.0 mmol) and AIBN (1.0 mmol). The solution was heated at 80 °C for 14 h under argon atmosphere. After the reaction, the mixture was

washed with sat. $NaHCO_3$ aqueous solution. The organic layer was dried over Na_2SO_4. After the removal of the solvent, the residue was chromatographed on silica gel to give 125 mg of 2-(1-adamantyl)-4-methylquinoline in 90% yield.

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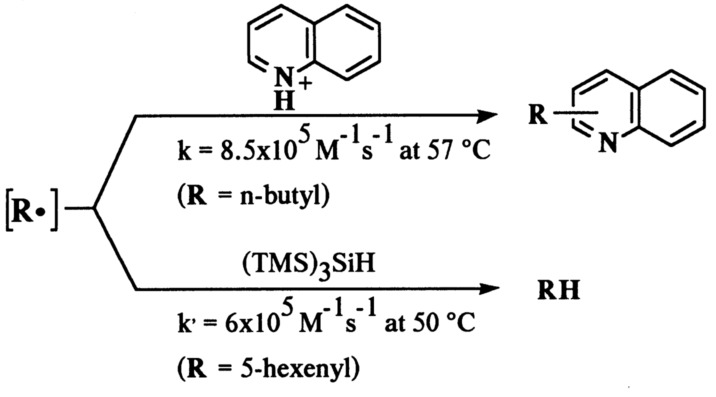

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