**Silylation of substituted pyridins**

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**Introduction**

A preliminary study on the reactivity of trimethylsilylconide anion Me₃Si⁻ (1) in HMPT (Shippey and Dervan, 1977) on haloaromatic compounds outlined concerns about the reaction mechanism involved, registering a dichotomy between electron-transfer (ET) in box and halogen-metal exchange (HME). These studies implied the reaction of PhX with 1 in HMPT, and revealed the occurrence of two intermediates, aryl radical and phenyl anion. trimethylsilylconide anion is usually generated by the reaction of sodium methoxide in hexamethyldisilane (Sakurai *et al.*, 1971; Sakurai and Kondo, 1975; Buncel *et al.*, 1992).

We have recently reported a new substitution mechanism of non-activated aromatic nucleus with silicon anions, especially Me₃Si⁻ (1) (Postigo and Rossi, 2001). These anions substitute a hydrogen of the aromatic nucleus by trimethylsilane group, without needing the presence of a classic leaving group, such as halogen. For example, pyridine reacts with 1 in HMPA to render 99% of 4-trimethylsilylpyridine. At short time reaction a dihydroderivative (4-trimethylsilyl-1,4-dihydropyridine, 92%; Fig. 1) is obtained.

![Figure 1](image)

The mechanism of this reaction was studied, S⁺N₁²⁻type reactions, benzine mechanism and classic S⁺N₆ nucleophilic substitution being discarded. These substrates react via the mediation of either a Meissenheimer complex or σ₁ pyridine (Fig. 2).

Fluorobenzene gives 71% of o- and p-fluorotrimethylsilylbenzene and 14% of trimethylsilylbenzene (2) in the same solvent (Fig. 3). Owing to the high reactivity of 1 toward these compounds, the reaction with benzene was investigated, thus giving 48% of 2.
Benzene and fluorobenzene show pronounced kinetic isotopic effects (1.65 and 3.2, respectively).

We have also studied the reactions of haloaromatic compounds with Me$_3$Si$^-$ in HMPA (Postigo and Rossi, 2001) (Fig. 4). In these compounds the benzine mechanism (bromomesitilene reacts to yield 2,4,6-trimethylsilylbenzene, 48%), $S_{RN}$ mechanism (Benkeser and Severson, 1951; Brook and Wolfe, 1957; Gilman and Wittenberg, 1958; Yammal et al., 1992, 1996; Lockhart et al., 1999; Córsico and Rossi, 2000 a,b) ($p$-chlorotrimehtylsilylbenzene is an intermediate), and the simple aromatic nucleophilic substitution (substrates do not contain activating groups of the classic nucleophilic substitution, such as nitro groups) were discarded.

Experiments are needed to elucidate the involvement of IMH and/or TE mechanism in box in the reactions of PhX with 1 in HMPA.
Figure 5. Relative yields concerning the disappearance of 3 and the formation of 4 and 5 in HMPA versus time.

In our laboratory we have provided mechanistic evidences to support the reaction mechanism proposed (Postigo et al., 2002 a,b). Therefore, we have extended the treatment of 1 with other heteronucleus, such as indole derivatives, where we observed substitution at position 2 (Fig. 6).

Figure 6

Results
To extend the applicability of this synthetic tool we have devoted to the silylation of substituted pyridines under reaction with 1 in HMPA. Silylated pyridines are very useful as synthetic intermediates in cross-coupling reactions with electrophilic agents, catalyzed by Pd (Fig. 7). The following pyridinic compounds were reacted with the trimethylsilyconide anion 1 in HMPA: 2-methylpyridine, 2-methoxypyridine, and 2,2'-dipyridyl. In all cases substitutions in position 4 were found. Pyridines with activating substituents, electron donors (2-methoxypyridine) were the least reactive, while 2,2'-dipyridyl, where pyridyl group behaves as electron withdrawing group, was the most reactive nucleus.

Figure 7
Experimental

The reactions were carried out in 25-ml grind-tubes, each fitted with septum and magnetic stir bar. The synthesis of 2-methyl-4-trimethylsilyl-pyridine is described as example.

A grind tube covered with a septum and fitted with a stir bar was subjected to vacuum (via cannula) for 5 minutes, was filled with nitrogen atmosphere, further vacuum, and then was flamed in order to eliminate rests of humidity. This procedure was repeated thrice. Once the appropriate inert atmosphere was achieved, 7.5 ml of HMPA were added under N\textsubscript{2} atmosphere (in the reaction with 2,2-bipyridyl 9.5 ml were injected).

After adding the solvent, vacuum was performed again; the tube was flamed, until the solvent began to boil. It was kept to cool for a few minutes and then kept under N\textsubscript{2} atmosphere. Then, 7.5 x 10\textsuperscript{-3} mols of sodium methoxide were added (in the case of reaction with 2,2-bipyridyl 0.015 mols were added), and again vacuum was established, then filled with N\textsubscript{2}. This procedure was repeated thrice.

The reaction tube was previously placed in an ice bath, and 7.0 x 10\textsuperscript{-3} mols HMDS were added by syringe (in the case of reaction with 2,2-bipyridyl 0.014 mols were added). The reaction was slightly exothermic at the bath temperature. The reaction mixture was kept under stirring for 20 minutes to allow anion development, thus giving an intense orange colour. When appearing the characteristic ion colour the tube was covered with an aluminum foil. Then, 2.5 x 10\textsuperscript{-3} mols of the substrate were added through syringe, immediately developing a deep dark red, which was kept until neutralization. The reaction was kept forward for two hours. The work-up consisted in neutralization of the crude reaction with saturated solution of ammonium nitrate, and two successive extractions with n-pentane (15 ml).

The organic phase was washed twice with distilled water (15 ml) to remove remanents of HMPA. The separation was performed by TLC of silicagel. The elution solvent was hexane:ethyl acetate (80:20). The yield of crude product was 45% (50% for 2,2-bipyridyl, and 39% in the case of 2-methoxypyridine as substrate), while the isolated compound was obtained in a 25% yield (67% of 4-(trimethylsilyl)-2-(4-trimethylsilyl)-pyridinyl)pyridine, 9% of 2-methoxy-4-trimethylsilylpyridine). Usual spectroscopic analysis (\textsuperscript{1}H-NMR, GC-MS) confirmed the identity of the product, 2-methyl-4-trimethylsilylpyridine.

Conclusions

Silylated pyridines are of high importance in organic chemistry as substrates for Pd-catalyzed cross-coupling reactions with electrophilic agents. In this work, we have extended the applicability of previously proposed reaction mechanisms to new pyridine derivatives without leaving groups. The work will continue with the silylation of other pyridinic nucleus, such as N-oxidopyridine and derivatives as well as pyrimidine and derivatives. It is worth to mention that our synthetic approach does not require substrates with classic leaving groups (halogens) to perform substitution. Therefore, it is not necessary to carry out the reaction with chlorinated or brominated nucleus as reagents.

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References

- Sakurai H. and Kondo F. (1975) Chemistry of organosilicon compounds: LXXX. Useful


