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NUCLEOPHILIC SUBSTITUTION REACTION OF α-SILOXYAMINES WITH ORGANOMETALLICS: A NEW METHOD FOR α-SUBSTITUTION OF TERTIARY AMINES VIA THEIR N-OXIDES

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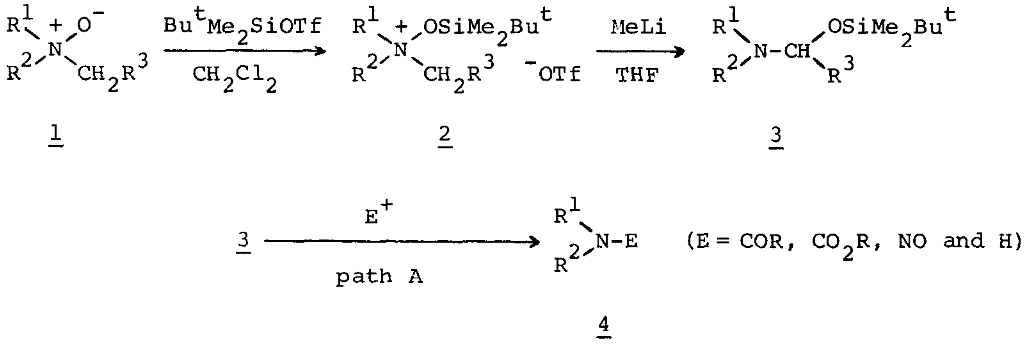
Summary: α-Siloxyamines obtained from tertiary amines via their N-oxides react with Grignard reagents and trialkylaluminums to afford new tertiary amines having an α-substituent derived from the organometallics.

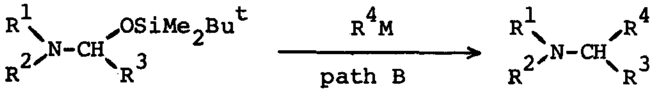
The carbon-carbon bond formation at the α-position of amines is one of the most important problems in the syntheses of nitrogen-containing natural products such as alkaloids. Although the electrophilic α-substitution method has been developed extensively in recent years using dipole-stabilized α-lithioamines,[1-3] the nucleophilic counterpart is still limited especially for the functionalization of tertiary amines.[4]

Recently, we have reported a new general method for dealkylation of tertiary amines via their N-oxides (1).[5] Thus, siloxyammonium salts (2) prepared form tertiary amine N-oxides and trialkylsilyl trifluoromethanesulfonate undergo rearrangement in the presence of strong bases[6] to give α-siloxyamines (3), which can be converted into various secondary amine derivatives (4) with appropriate electrophiles (path A).

In this paper we delineate the reaction of α-siloxyamines (3) with some organometallics leading to substitution of the siloxy group by alkyl, alkenyl, or aryl group (path B).



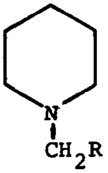
(E = COR, CO_2R, NO and H)



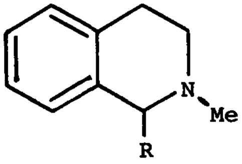
3 5

Thus, treatment of the siloxyamines (3) obtained in situ from 1 with Grignard reagents or trialkylaluminums afforded α-substitution products (5) in moderate to good yields. Although the reactions of 3 with alkyllithiums were also examined, desired substitution reaction did not occur perhaps due to the rather lower affinity of lithium reagents with oxygen atom of the siloxy group than that of magnesium and aluminum reagents.

A typical example is as follows. N-Methylpiperidine N-oxide (1a) (1 mmol) was allowed to react with t-butyldimethylsilyl trifluoromethanesulfonate (1.1 mmol) in dichloromethane to give 2a. After replacement of the solvent by tetrahydrofuran, 2a was treated with methyllithium (1.2 mmol) at 0 °C and then, after once more replacement of the solvent into toluene, with phenylmagnesium bromide (1.5 mmol) at room temperature to afford the amine 5a (R= Ph) in 74 % yield. When the Grignard reagent was added without the solvent exchange into toluene, the yield of 5a was somewhat diminished (58 %). Results obtained from the reactions of 1a, N-methyl-1,2,3,4-tetrahydroisoquinoline N-oxide (1b), and tribenzylamine N-oxide (1c) with Grignard reagents or organoauminums are summarized in Table.[7]



5a



5b

Of particular note among these results is the accomplishment of the α-substitution of amines by phenyl and vinyl groups with sp^2 carbon as a reacting center, since the introduction of such groups is difficult in the electrophilic substitution using α-lithioamine synthetic equivalents. In the reactions of 3b with Grignard reagents, the substitution was executed more effectively when 3b was treated with trimethylsilyl trifluoromethanesulfonate (1.2 equiv.) before the addition of Grignard reagents, the yield of 5b otherwise being decreased to some extent.[8] In contrast to the reactions with Grignard reagents, those with trialkylaluminums gave α-substituted amines in good yields without replacement of the solvent into toluene.

In view of ready availability of amine N-oxides and a wide variety of Grignard and organoaluminum reagents, the present one-pot sequence provides a new convenient method for nucleophilic α-substitution of tertiary amines.

Table. α-Substitution of Tertiary Amines via Their N-Oxides.

N-oxide	RM[a]	Product	Yield (%)[b]
(1a)	PhMgBr	(5a) [R = Ph]	74 (80)[c]
(1a)	CH_2=CHMgBr	(5a) [R = CH=CH_2]	51
(1a)	$PhCH_2MgBr$	(5a) [R = CH_2Ph]	52 (71)
(1a)	EtMgBr	(5a) [R = Et]	47
(1b)	PhMgBr	(5b) [R = Ph]	56
(1b)	CH_2=CHMgBr	(5b) [R = CH=CH_2]	54
(1b)	EtMgBr	(5b) [R = Et]	41
(1a)	$Bu^i{}_3Al$	(5a) [R = Bu^i]	45
(1a)	Et_3Al	(5a) [R = Et]	69 (91)
(1c)	Et_3Al	$(PhCH_2)_2NCH(Et)Ph$	75

a) The Grignard reagents were prepared in tetrahydrofuran and trialkylaluminums were used in hexane solution.

b) Isolated yield after alumina column chromatography.

c) Values in parentheses denote the NMR yields.

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References and Notes

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2. D. Seebach and D. Enders, Angew. Chem. Int. Ed. Engl., 14, 15 (1983); D. Seebach, J. J. Lohman, M. D. Syfrig, and M. Yoshifuji, Tetrahedron, 39, 1963 (1983) and references cited therein.
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4. T. Shono, Y. Matsumura, and K. Tsubata, J. Am. Chem. Soc., 103, 1172 (1981); L. E. Overman and R. M. Burk, Tetrahedron Lett., 25, 1635 (1984) and references cited in these reports.
5. Demethylation, deethylation, and debenzylation were achieved for either cyclic or acyclic tertiary amines via the corresponding α-siloxyamines: R. Okazaki and N. Tokitoh, J. Chem. Soc., Chem. Commun., 192 (1984).
6. Either alkyllithiums or lithium diisopropylamide can be used as a base, methyllithium being most effective.
7. All the products described here gave the satisfactory spectral and/or analytical data (^{1}H-NMR, ^{13}C-NMR, and exact mass analysis).
8. For example, 3b was treated directly with phenylmagnesium bromide in tetrahydrofuran to afford 5b (R = Ph) in 47 % yield.

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