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A CONVENIENT PROCEDURE FOR THEREDUCTION OF AMINOACIDS AND AMIDES USING TETRABUTYLAMMONIUM FLUORIDE AND POLYMETHYLHYDROSILOXANE

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ABSTRACT
A range of α-aminoacids**(1a-1h)**have been converted efficiently to the corresponding β-aminoalcohols: 2-amino-3-methylpentan-1-ol (isoleucinol) **(2a)**, 2-amino-4-(methylthio)butan-1-ol (methioninol) **(2b)**, 2-amino-3-methylbutan-1-ol (valinol) **(2c)**, 2-amino-3-(4'-hydroxyphenyl) propan-1-ol (tyrosinol) **(2d),** 2-amino-3-phenylethan-1-ol (phenylglycinol) **(2e)**, 2-amino-3-phenylpropan-1-ol (phenylalaninol) **(2f),** 2-aminoethan-1-ol (glycinol) **(2g),** and 2-aminopropanol-1-ol (alaninol) **(2h)**, with polymethylhydrosiloxane, PMHS, in the presence of catalytic tetrabutylammonium fluoride, TBAF with > 61% yield. Carboxylic acids and their derivatives such as amides**(3a** and **3b)** have also been reducedto the corresponding amines: N-ethylaniline**(4a)** and N-methylaniline**(4b)** with polymethylhydrosiloxane, PMHS, in the presence of catalytic tetrabutylammonium fluoride, TBAF with > 74% yield.
Key words: Reduction, PMHS, TBAF, α-aminoacids, amides.

1-INTRODUCTION
There is a considerable interest in efficient routes to reducecarboxylic acids and their derivativessince it is one of the most important, fundamental and practical reactions. In 1991 Buchwald's group have used PMHS in combination with Cp_2TiCl_2, n-BuLi for the reduction[i-iii]. This was followed by the description of use of PMHS and titaniumisopropoxide, again for the reduction of esters[iv]. In related papers the use of polymethylhydrosiloxanein combination with TBAF has been studied[v-xi]. These processes, which are usually carried out in polar solvents such as DMSO or DMF, are described as heterogeneous and generally require an excess of fluoride. In 1980's Corriu and Co-workers have shown that esters may be reduced with PMHS by fluoride or alkoxide-induced hydrosilylation[ix].

In 1990's, N. J. Lawrence and Co-workers described the efficient reduction of esters to alcohols with polymethylhydrosiloxane (PMHS) [$Me_3SiO(Me_3HSiMe_3)_nSiMe_3$] in the presence of titanium isopropoxide or zirconium alkoxide[iv, xii, xiii]. This was followed by the description of the use of PMHS and catalytic fluoride[xiv].

We recently described the efficient reduction of glycine and alanine to aminoalcohols with polymethylhydrosiloxane (PMHS) in the presence of catalytic tetrabutylammoniumfluoride[xv].We now report that the same transformation can be achieved but this time with an extension to a range of α-aminoacidsand carboxylic derivatives such as amides using tetrabutylammonium fluoride and polymethylhydrosiloxanewith some modifications.

2-EXPERIMENTAL

2.1- Methods

All reactions were carried out under atmospheric air conditions. Solutions were dried over anhydrous magnesium sulphate ($MgSO_4$) and evaporated under reduced pressure using a rotary evaporator (rotary evaporator (IKA Evaporator RV 06-ML). Solvents were purified according to standard methods.

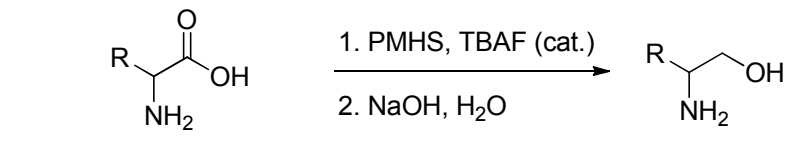
2.2- Physical measurements

^{1}H NMR spectra were recorded on BRUCKER AC 400 MHz spectrometer at 0°C, and the chemical shifts are reported in ppm relative to the central line of the singlet for $CDCl_3$ at 7.26 ppm. Coupling constants (*J* values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).^{13}C NMR and DEPT were recorded on BRUCKER AC 101 MHz spectrometer at 0°C and all are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77.16 ppm. The spectra reported are proton decoupled.

IR spectra were recorded on SHIMADZU 830-FTIR spectrometer using KBrpellets.Melting points were recorded on a Gallenkamp melting point apparatus, and are uncorrected.Thin layer chromatography (TLC) was performed on precooked 0.25 mm silica gel plates 60F254purchased from Merck.

2.3-Standard procedure

To a stirred mixture of amino acid or amide(1 mmol) and tetrabutylammoniumfluoride (0.02 mmol) in dry tetrahydrofuran (3 mmol). The mixture was stirred at room temperature until the reaction was complete (by TLC). Sodium hydroxide (5ml of a 3N solution) was added dropwise. After stirring vigorously overnight the solution was extracted with dichloromethane (3X150 ml). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated *in Vacuo*. The residue was purified chromatography (SiO_2). Typical pure yield after purification is (58-80%)**(Scheme-1).**

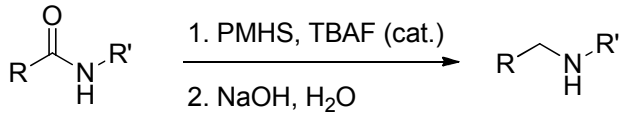


1a: R= $CH_3CH_2(CH_3)CH$—
1b: R= $CH_3SCH_2CH_2$–
1c: R=$(CH_3)_2CH$—
1d: R= HO–C$_6$H$_4$–CH_2–
1e: R= Ph-
1f= R= $PhCH_2$
1g: R= H
1h: R= CH_3-

2a: R= $CH_3CH_2(CH_3)CH$—
2b: R= $CH_3SCH_2CH_2$–
2c: R=$(CH_3)_2CH$—
2d: R= HO–C$_6$H$_4$–CH_2–
2e: R= Ph-
2f= R= $PhCH_2$
2g: R= H
2h: R= CH_3-

Scheme-1: Reduction of aminoacids to their corresponding alminoalcohols

The protocol is also an efficient method for the reduction of carboxylic acid derivatives such as amides to the corresponding amines**(Scheme-2).**



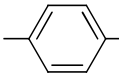
3a: R= CH_3–
R'= ph
3b: R= H
R'= ph

4a: R= CH_3–
R'= ph
4b: R= H
R'= ph

Scheme-2: Reduction of amides to their corresponding amines

The results are summarized in **Table-1**

Table 1: Yields for the reduction of substituted aminoacids **1** and amids **3**

Aminoacids		Amides		
R	**Yield (%) 1 ⟶ 2**	**R**	R'	**Yield (%) 3 ⟶ 4**
$CH_3CH_2(CH_3)CH$—	67.47	—H	—Ph	75.16
$CH_3SCH_2CH_2$–	61.03	–CH_3	—Ph	74.13
$(CH_3)_2CH$—	85.14			
HO—  —CH_2–	58.14			
Ph—	65.30			
$PhCH_2$—	70.20			
H—	75.20			
CH_3–	80.65			

The amino alcohols **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h, 4a** and **4b** were identified by the following spectroscopic data:

2.3.1- 2-amino-3-methylpentan-1-ol(isoleucinol) (2a):

(Oil, Yield 67.47%; IR(ν cm^{-1}): 3396.4 (L,$\nu_{OH\ et\ NH2}$) ; 2875.7- 2960.5 (F,ν_{C-H}) ; 1656.7(F,ν_{N-H}), 1463.9(F,ν_{C-O-H}), 1029 (F,ν_{C-O}), 850 (f ,ν_{NH2}); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (1H, s, -OH), 3.24 (2H, m, $\underline{CH_2}OH$), 1,73 (1H, m, $\underline{CH}$-NH_2), 1.57 (2H, s, NH_2),1.33 (2H, m, $CH\underline{CH_2}CH_3$), 1.14 (1H, m, $CH_2\underline{CH}CH_3$), 0.88 (6H, m, 2 -CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) 66.39 (-CH_2OH), 57.39 [-$CH(NH_2)$], 52.15 (-CH-), 22.57 ($\underline{-CH_2}CH_3$), 18.22 (CHCH3), 12.16 ($CH_2\underline{CH_3}$).

2.3.2-2-amino-4-(methylthio)butan-1-ol(methioninol) (2b):

Yield: 61.03%; IR(ν cm^{-1}): 3398.3 (L,$\nu_{OH\ et\ NH2}$) ; 2873.7- 2935.5 (F, ν_{C-H}) ; 1662.5 (F, ν_{N-H}) ; 1465.8(F,ν_{C-O-H} ; 1029.9 (F, ν_{C-O}) ; 883.3 (f, ν_{NH2}) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (1H, s, OH), 3.35 (2H, m, $\underline{CH_2}OH$), 2.10-2.09 (1H, m, $\underline{CH}$-NH_2), 1.68 (2H, m, S-$\underline{CH_2}$), 1.47 (3H, *m*, S-$\underline{CH_3}$), 1.01 (4H, t, *J* = 7.3 Hz, NH_2 and CH-$\underline{CH_2}$-CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 58.83 (-CH_2OH), 24.00 (-CH(NH2)), 19.66 (-CH2-S-), 15.05 (-CH_2-), 13.59 (CH_3).

2.3.3- 2-amino-3-methylbutan-1-ol (valinol) (2c)

Yield: 85.14%; IR (ν cm^{-1}): 3400. (L, $\nu_{OH\ et\ NH2}$) ; 2873.7- 2960.5 (F, ν_{C-H}) ; 1558.4 (F, ν_{N-H}), 1488.9 (F, ν_{C-O-H}), 1033.8 (F, ν_{C-O}) ;883.3 (f,ν_{NH2}); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (1H, dt,

J^2=10.68Hz, J^1=2.64 Hz, $\underline{CH_2}OH$), 3.18 (1H, t, *J*=7.3Hz, $\underline{CH_2}OH$), 2.73 (2H, S, NH_2), 2.43 (1H, m, $\underline{CH}NH_2$), 1.48 (1H, m, $CH(CH_3)_2$), 0.78 (6H, dd, J^1=6.97 Hz, J^2=3.85 Hz, 2 -CH_3) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 64.32 (CH_2OH), 58.30 [-$CH(NH_2)$], 30.81 [-$CH(CH_3)_2$], 19.23 (-CH_3), 18.25 (-CH_3).

2.3.3-2-amino-3-(4'-hydroxyphenyl) propan-1-ol (tyrosinol) (2d):

Yield 58.14%; IR (ν cm^{-1}): 3360-3300. ($\nu_{OH\ et\ NH2}$); 2873.7- 2935.5 (F, ν_{C-H}) ; 1662.5 (F, ν_{N-H}) ; 1465.8 (F,ν_{C-O-H}; 1029.9 (F, ν_{C-O}) ; 883.3 (f, ν_{NH2});^{1}H NMR ($CDCl_3$; 400 MHz): δ (ppm): 2.7 (1H, m, $C_6H_4\underline{H}CH$), 2.9 (1H, m, $C_6H_4HC\underline{H}$), 3.1 (1H, m, -$\underline{H}CHNH_2$), 3.2 (1H, m, -$\underline{H}CHOH$), 3.5 (1H, m, -HC$\underline{H}$OH), 3.6 (1H, m, OH), 5.1(2H, s, brs, NH_2), 5.3(1H, s, $C_6H_4\underline{OH}$), 6.7 (2H, m, 3, 5 Ar-H), 7.1 (2H, m, 3, 5 Ar-H); ^{13}C NMR($CDCl_3$; 101 MHz): δ155.8 (C, Ar-OH)); 130.7 (3, 5 C, Ar); 116.2 (2, 6 C, Ar); 64.9 ($\underline{C}H_2OH$); 53.9 ($\underline{C}$-NH_2); 39.6 (C_6H_5-$\underline{C}H_2$).This aminoalcohol was identified by comparison its spectra with that of an authentic sample[xiv].

2.3.4-2-amino-3-phenylethan-1-ol (phenylglycinol) (2e):

^{1}H NMR ($CDCl_3$; 400 MHz): δ(ppm): 2.0 (3H, s, brs,NH_2, OH), 3.5 (1H, t, *J*=8.3 Hz, $CHNH_2$), 3.7 (1H, dd, J=8.3, 4.2 Hz, HCHOH), 4.1 (1H, dd, *J*=8.3, 4.2 Hz, HCHOH), 7.2-7.5 (5H, m, Ar-H); ^{13}C NMR($CDCl_3$; 75 MHz): δ 58.3 (CH); 67.7 (CH_2); 127.5 (CH, Ar); 128.4 (CH, Ar); 129.5 (CH, Ar); 142.0 (C, Ar). This aminoalcohol was identified by comparison its spectra with that of an authentic sample[xvi].

2.3.5-2-amino-3-phenylpropan-1-ol (phenylalaninol) (2f):

m.p. 90-92°C [lit.[xviii]m.p. 90-92°C)];IR (ν cm^{-1}): 3360-3300. ($\nu_{OH\ et\ NH2}$); ^{1}H NMR ($CDCl_3$; 400 MHz): δ (ppm): 1.5-2.1 (3H, s, brs, NH_2, OH), 2.5 (1H, dd, *J*=13, 9 Hz, $HCHC_6H_5$), 2.8 (1H, dd, *J*=13, 9 Hz, $HCHC_6H_5$), 3.1 (1H, m, $CHNH_2$), 3.5 (1H, dd, *J*=11,7 Hz, HCHOH), 4.1 (1H, dd, *J*=11,7 Hz, HCHOH), 7.1-7.4 (5H, m, Ar-H); ^{13}C NMR($CDCl_3$; 101 MHz): δ40.4 ($PhCH_2$); 54.0 (CH); 65.9 (CH_2OH); 126.5 (CH, Ar); 128.4 (CH, Ar); 129.0 (CH, Ar); 138.0 (C, Ar); m/z (FAB): 466 (24), 311 (4), 303 [(2M+H),$^+$ 11], 285 (9), 152 [(M+H),$^+$ 100], 136 [(M-OH),$^+$5], 120 (21), 105 (10), 91 (55).This aminoalcohol was identified by comparison its spectra with that of an authentic sample[xvi].

2.3.6-2-aminoethan-1-ol (glycinol) (2g):

IR (ν cm^{-1}): 3360-3300. ($\nu_{OH\ et\ NH2}$); ^{1}H NMR ($CDCl_3$; 400 MHz): δ (ppm): 1.1 (3H, m, CH_3), 2.8 (2H, t, *J*=8.0 Hz, CH_2NH_2), 3.7 (2H, t, CH_2OH); ^{13}C NMR($CDCl_3$; 101 MHz): δ 40.0 (CH_2NH_2); 63.7 (CH_2OH)[xv].

2.3.7-2-aminopropanol-1-ol (alaninol) (2h):

IR (ν cm^{-1}): 3360-3300. ($\nu_{OH\ et\ NH2}$); ^{1}H NMR ($CDCl_3$; 400 MHz): δ (ppm): 2.0 (3H, s, brs,NH_2, OH), 2.0(3H, s, brs,NH_2, OH), 3.0 (1H, m, $CHNH_2$), 3.7 (1H, m, HCHOH), 3.9 (1H, m,HCHOH); ^{13}C NMR($CDCl_3$; 101 MHz): δ 20.0 (CH_3); 50.8 (CH), 127.5 (CH_2)This aminoalcohol was identified by comparison its spectra with that of an authentic sample[xvi].

2.3.4-N-ethylaniline (4a):

Yield 75.64%;IR (ν cm^{-1}): 3259.5-3300 (L , ν_{NH}) ; 3050 (m, ν_{C-H}) ; 2950 (m, ν_{C-H}) ; 1608.8-1662.5 (F,νc=c) ; 1598.9(F,ν_{N-H}) ; 1263.3 (m, ν_{C-N}) aryl ; 752.2 (F,ν_{NH});^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, m, NH), 7.12 [2H, t, *J* = 7.9 Hz, C_3 and C_{3*}(ph)], 6.72 [1H, t, *J* = 7.26 Hz, C_4(ph)], 6.56 and 6.62 [2H, dd, *J* = 1.09 Hz, *J* = 7.46 Hz, $2C_2$ and C_{2*}(ph)], 3.53 (2H, m, CH_2),

1.42 (3H, t, CH_3);^{13}C NMR (101 MHz, $CDCl_3$) δ146.55 [1C, NH-C_1(ph)], 129.33 [2C, $C_3$and C_{3*}(ph)], 118.52 [1C, C_4(ph)], 115.21 [2C, $C_2$and C_{2*}(ph)], 23.96 (1C, CH_2-NH), 13.71 (1C, CH_3).

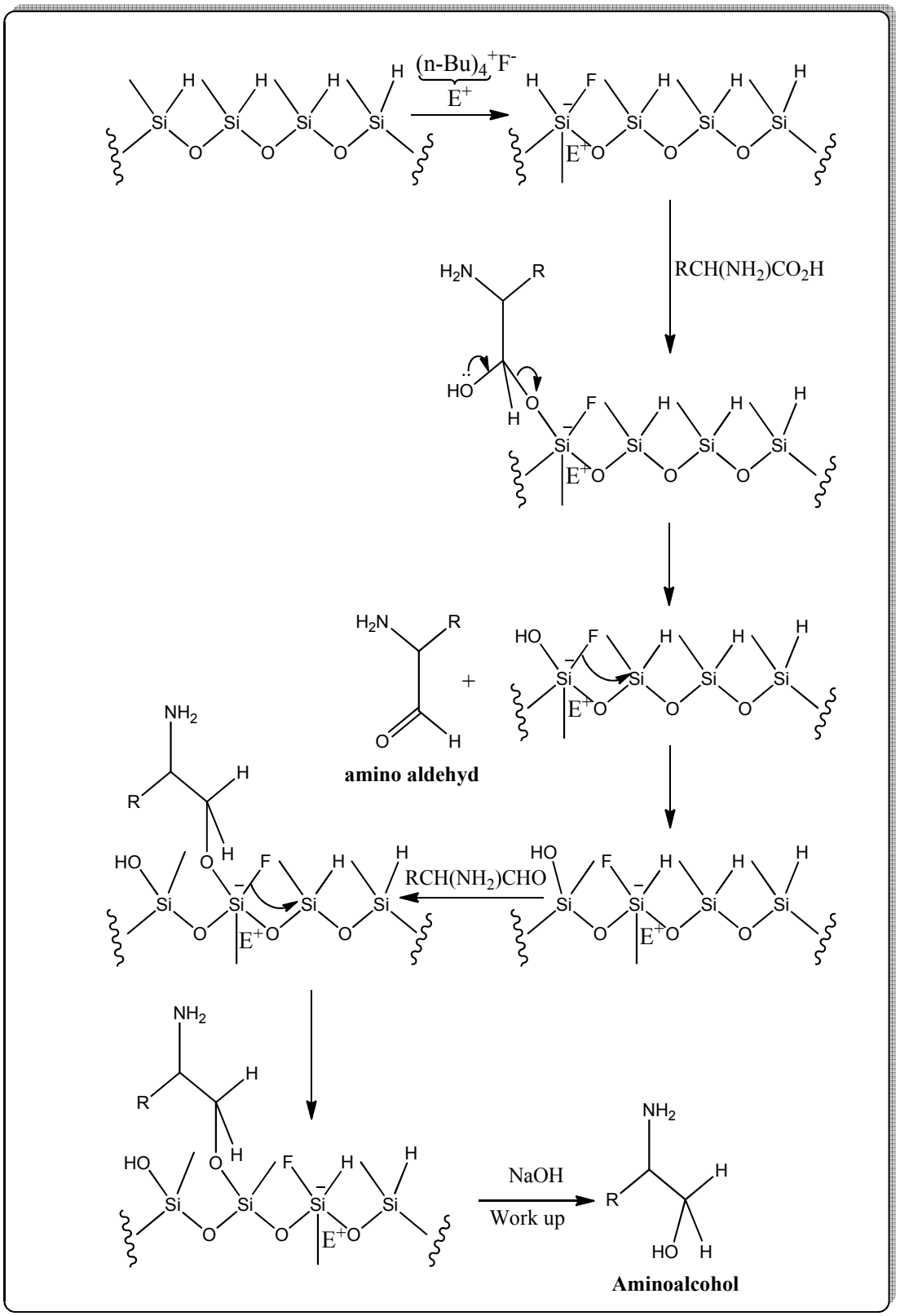
2.3.5-N-methylaniline(4b):

Yield 74.13%; IR (ν cm^{-1}): 3355.9 (L,ν_{NH}) ; 3035.7 (m,ν_{C-H}) ; 2873.5- 2950 (m,ν_{C-H}); 1608.8-1620.1 (F,νc=c) ; 1498.6(F,ν_{N-H}) ; 1278.7 (F,ν_{C-N}) aryl ; 752.2 (F,ν_{NH}); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (1H, s, NH), 7.44 [2H, d, *J* = 7.76 Hz, 2C_2 and C_{2*}(ph)] 7.09 [2H, t, *J* = 7.91 Hz, C_3 and C_{3*}(ph)], 6. 90 [1H, t, *J* = 7.39 Hz, C_4(ph)], 3.60 (3H, m, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.25 [1C, NH-C_1(ph)], 127.31 [2C, C_3 and C_{3*}(ph)], 122.58 [1C, C_4(ph)], 118.96 [2C, C_2 and C_{2*}(ph)], 66.53 (1C, CH_3).

3-RESULTS AND DISCUSSION

As part of our studies on the reduction of aminoacids with PMHS, we found that catalytic tetrabutylammonium fluoride (TBAF) (0.02 mole %) is a remarkable homogeneous catalyst for this process[xv].

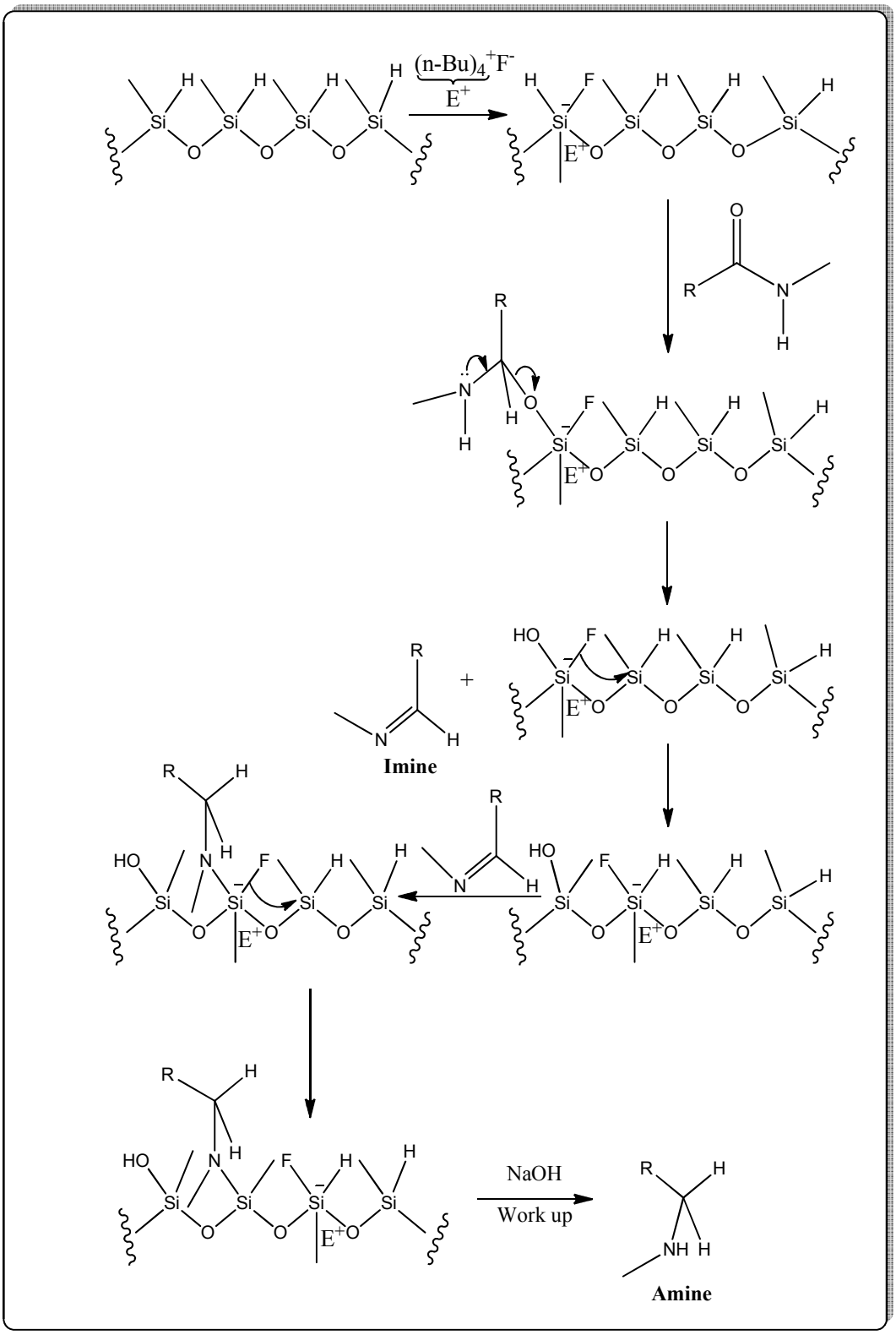
As expected two equivalents of Si-H are required for the reduction one aminoacid to the corresponding aminoalcohol: The first to reduce an aminoacid to an aminoaldehyde, and the second to reduce an aminoaldehyde to an aminoaldehyde. The impressive rate acceleration is possibly due to the interamolecular transfer of nucleophile from the silicate to another silicon atom, as illustrated in **Scheme-3** via 1,3-mode of transfer, a process that is repeated over and over again as the nucleophile travels along the polymer backbone[xvi]. The corresponding process of nucleophile transfer in an intermolecular sense is presumably much slower. This process is called "Zipper"catalysis, in detail[xii].



Scheme-3: Proposed mechanism of nucleophile-promoted "zipper catalysis"

Reduction of carboxylic acids and their derivatives such as amides has been examined with a variety of complex metal hydrides and metal hydrides such as lithium aluminium hydride, lithium trimethoxyaliminohydride, etc[xvii, xviii]. The most common reagent, lithium aluminium hydride, has been widely applied to such reductions.

In 1994, J.W. Simek and Co-workers described the efficient reduction of carboxylic acid group to alcohols using $NaBH_4$ method with either electrophile can be modified to any scale; the use of I_2 as the electrophile performed better at the semi- micro scale than the H_2SO_4method[xviii].
In our protocol, the use of polymethylhydrosiloxane, PMHS, providesr an alternative method forthe reduction of carboxylic acids and their derivatives.For such reduction, PMHS, can often successfully applied unlike diborane for such reductions occurs with unsaturated derivatives, such as N,N-dimethyl cinnamamide,since dborane rapidly adds to double bond.
Stoichiometrically, two hydrides are required to reduce one amide to the corresponding amine: The first to reduce an amide to the corresponding imine, and the second to reduce an imine to an amine**(Scheme-4)**. As is typical for PMHS reactions, a significant excess of reagents is used to assure complete reduction.



Scheme-4: Proposed mechanism of nucleophile-promoted "zipper catalysis"

3-CONCLUSION

In summary, we have shown that polymethylhydrosiloxane in combination with catalytic TBAF is an excellent reducing agent for the mild reduction of aminoacids and carboxylic derivatives such as amides.

4-ACKNOWLEDGMENT

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