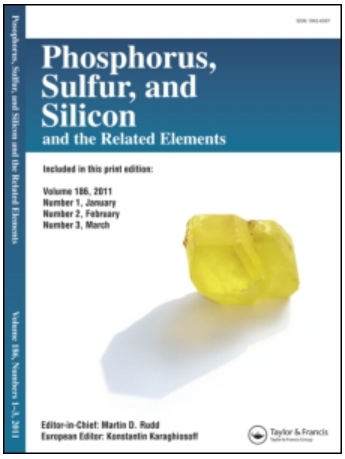

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Triethyl Phosphite in Organic Synthesis. A Facile, One-Pot Conversion of Alcohols into Amines

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TRIETHYL PHOSPHITE IN ORGANIC SYNTHESIS. A FACILE, ONE-POT CONVERSION OF ALCOHOLS INTO AMINES

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Abstract: General protocols for converting primary, secondary, and tertiary alcohols into the corresponding primary amines are presented.

INTRODUCTION

Activation of alcohols followed by nucleophilic displacement of an oxy anion by azide and subsequent reduction constitutes an efficient route for the synthesis of primary amines. A recent review has updated the rich scope of azide chemistry and provided exhaustive coverage of methods for reduction of azides to amines[1]. Among the spectrum of these methods the Staudinger reaction evidently plays an important role due to its high effectiveness and chemoselectivity. Triphenylphosphine has been insofar notoriously used for transforming azides into amines[2,3] as well as for one-pot amination of alcohols by Mitsunobu azidation followed by Staudinger reduction[4]. The essential drawbacks of all these procedures is a high cost of triphenylphosphine, its relatively low nucleophilicity, and sometimes technical difficulties in separation and purification of an amine. Triethyl phosphite, a relatively inexpensive substitute of triphenylphosphine in Staudinger reaction, is recommended here as a reagent of choice, especially for large scale preparation of amines from alcohols. One-pot procedures, specific for primary, secondary, and tertiary alcohols, and involving judicious combination of known methods - activation of a hydroxy group, azidation, and Staudinger reaction followed by deprotection of an amino function are presented in this paper.

1.Conversion of primary alcohols into amines.

The following sequence was found to be the most convenient route from primary alcohol into the corresponding amine:

$$1^{0}\ R\text{-}OH \xrightarrow[\text{benzene. } 25\text{-}30^{0},\ 1\ h]{(CF_3CO)_2O/Et_3N} RO\text{-}\overset{\overset{O}{\|}}{C}\text{-}CF_3 \xrightarrow[3\ h,\ \text{reflux}]{NaN_3/\text{benzene-DMSO}(1:2)}$$

$$\longrightarrow R\text{-}N_3 \xrightarrow[25\text{-}30^{0},\ 4\ h]{(EtO)_3P} R\text{-}N{=}P(OEt)_3 \xrightarrow[6\ h,\ \text{reflux}]{PTSA.H_2O/EtOH.} R\text{-}NH_3^{+}TsO^{-}$$

Trifluoroacetylation in the presence of an equimolar amount of triethylamine is followed by conventional azidation of alkyl trifluoroacetate and Staudinger reaction of the azide with triethyl phosphite to produce,after loss of nitrogen, a triethoxyiminophosphorane intermediate. This is easily deprotected by refluxing with p-toluenesulfonic acid monohydrate in ethanol to give the respective amine tosylate. It is neither necessary nor desirable to isolate and/or purify any intermediately formed compounds. Deprotection of N-alkyl triethoxyiminophosphoranes by means of p-toluenesulfonic acid is superior and more convenient to the previously described P-N bond cleavage with gaseous hydrogen chloride[5]. Primary alkylamine tosylates crystallize easily and can be isolated in analytically pure state.

2.Conversion of secondary alcohols into sec.-alkyl amines.

Trifluoroacetylation is totally unsuitable for activation of secondary alcohols prior to azidation. Instead,mesylation (essentially modified version of that described in the literature[6]) was found to be the procedure of choice. Azidation of crude mesylates can be effectively carried out in DMSO solution at 35-40^{0}.The reaction proceeds stereospecifically with complete inversion of the configuration of the alkyl group as proved by converting (S)-(+)-2-octanol into (R)-(-)-2-octanamine. Sec-alkyl azides are transformed into the corresponding triethoxyiminophosphoranes in usual way using triethyl phosphite.

Degradation of the latter by refluxing them with p-toluenesulfonic acid monohydrate in ethanol was,however, found inconvenient due to incomplete conversion even after prolonged heating. "Wet" deprotection of triethoxyiminophosphoranes with 20% hydrochloric acid and isolation of amines as their hydrochlorides is therefore recommended for sec-alkyl amines. The following scheme illustrates the procedure:

$$2^{o}\ R\text{-}OH \xrightarrow[CH_2Cl_2,5\text{-}20^{o}]{MsCl/Et_3N} R\text{-}O\text{-}Ms \xrightarrow[35\text{-}40^{o},6\ h]{NaN_3/DMSO} R\text{-}N_3 \longrightarrow$$

$$\xrightarrow[30\text{-}35^{o},4\ h]{(EtO)_3P} R\text{-}N{=}P(OEt)_3 \xrightarrow[reflux,2\ h]{20\%HCl} R\text{-}NH_3^{+}\ Cl^{-}$$

Conversion of tertiary alcohols into t-alkyl amines[7]

Transformation of tertiary alcohols into the corresponding azides via conventional activation of a hydroxyl group followed by nucleophilic displacement is impossible for obvious reasons. Such conversion can be, however, easily accomplished by means of trimethylsilyl azide in the presence of boron trifluoride etherate:

$$3^{o}\ R\text{-}OH \xrightarrow[benzene,r.t.,24h]{Me_3SiN_3/BF_3.Et_2O} R\text{-}N_3 \longrightarrow \longrightarrow R\text{-}NH_3^{+}\ TsO^{-}$$

Crude azides can be reduced to the corresponding amine tosylates via the respective N-alkyl triethoxyiminophosphoranes.

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TABLE Amine tosylates and hydrochlorides

Entry	R	Yield (%)[a]	M.p.
1.	C_4H_9	58	118-119°
2.	C_6H_{13}	64	124-125°
3.	C_8H_{17}	67	130-131°
4.	$Ph\text{-}CH_2$	78	179-180°
5.	$Ph\text{-}CH_2\text{-}CH_2$	65	174-175°
6.	$p\text{-}MeO\text{-}C_6H_4$	50	201-202°
7.	$HC{\equiv}C\text{-}CH_2$	75[b]	152-153°
8.	$CH_2{=}CH\text{-}CH_2$	64[b]	96- 97°
9.	2-pentyl	65[c]	152-153°
10.	cyclopentyl	74[c]	207-208°
11.	3-hexyl	61[c]	228-230°
12.	(S)-(+)-2-octyl	62[c]	90- 91°
13.	$(CH_3)_3C\text{-}$	59	202-203°
14.	$(CH_3)_2(CH_3CH_2)C\text{-}$	54	175-177°
15.	$(CH_3CH_2)_2(CH_3)C\text{-}$	29	143-144°
16.	$(PhCH_2)(CH_3)_2C\text{-}$	37	169-172°
17.		45	184-185°

[a]Overall yield of pure amine salt.
[b]Azidation was performed at 35-40° for 6h.
[c]Amine hydrochlorides.