Reduction of Some Functional Groups with Zirconium Tetrachloride/Sodium Borohydride

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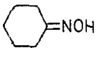
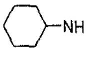
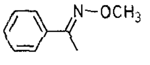
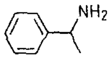
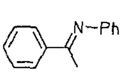
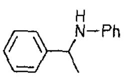
Novel reducing agent prepared from zirconium tetrachloride and sodium borohydride reduces various functional groups including C=O double bonds, C=N double bonds and C≡N triple bonds in excellent yield (85-96%) under mild condition.

A combination of sodium borohydride and transition-metal halides such as cobalt chloride,[1-3] nickel chloride,[4-6] titanium tetrachloride[7,8] or ferric chloride[9,10] has been frequently used in the selective reduction of various functional groups. For example, titanium reagents prepared from titanium tetrachloride and sodium borohydride[7] as well as lithium aluminum hydride have been widely used in organic synthesis. Hydrogenation of olefins with lithium aluminum hydride in the presence of zirconium tetrachloride has been also reported.[13] However, to our knowledge, zirconium tetrachloride has not been applied for making the combined reducing agent with sodium borohydride. We have now investigated the reducing properties of zirconium tetrachloride/sodium borohydride and have found that this reagent can be used to advantage for the reduction of the compounds including C=O double bonds, C=N double bonds and C≡N triple bonds.

$$C{=}O/C{=}N/C{\equiv}N \xrightarrow[85\text{-}96\ \%]{NaBH_4/ZrCl_2,\ THF,\ r.t.,\ 5\ h} CH_2/C{-}NH_2/C{-}NH_2$$

Table. Reduction with Zirconium Tetrachloride/Sodium Borohydride

Substrate	Product	Yield[a] (%)	bp (°C)/Torr	
			found	reported
PhCHO	$PhCH_2OH$	95	93/10	205.4/760[17]
$PhCOCH_3$	$PhCH(CH_3)OH$	96	85/10	203.6/745[17]
$PhCO_2H$	$PhCH_2OH$	85	93/10	205.4/760[17]
$PhCO_2Et$	$PhCH_2OH$	89	93/10	205.4/760[17]
$PhCH_2COCl$	$PhCH_2CH_2OH$	90	98-100/12	219-221/750[17]
$PhCONMe_2$	$PhCH_2NMe_2$	88	66-68/6	98/22[18]
		85	72-73/100	134.5/760[19]
		95	65-66/10	184.5/760[20]
		92	138-140/1	142/1.5[21]
$PhCH_2CN$	$PhCH_2CH_2NH_2$	91	62-63/4	90-93/15[22]
$PhNO_2$	no reaction[b]	–	–	–
PhBr	no reaction[b]	–	–	–

[a] Yield of isolated purified product.
[b] After 2 days.

As summarized in the Table, many different kinds of substrates were reduced easily with the combined reagent of zirconium tetrachloride/sodium borohydride in good yield under mild reaction condition. Treatment of acetophenone with a mixture of zirconium tetrachloride (1.25 equiv) and sodium borohydride (5 equiv) in tetrahydrofuran at room temperature for 5 h affords 1-phenylethanol in nearly quantitative yield. Roughly the same procedure was used for all reactions. This reagent reduces carboxylic acids, carboxylic esters, acyl chlorides, carboxamides, oximes, and nitriles, which cannot be reduced or may be reduced very slowly, with sodium borohydride alone. In the case of reduction of *tert* amides, oximes, and nitriles longer reaction time (20 h) was required to give reasonable yields. Although lithium aluminum hydride can reduce oximes to afford amines in low yield, aziridines are obtained as side product in some cases.[14] Diborane reduction of oximes usually affords hydroxylamines.[15] In order to obtain the corresponding primary amines high temperature is required.[16] Our reagent reduces oximes smoothly to give primary amines without any side reactions, while nitrobenzene and bromobenzene were found to be inert. This reagent is considered to be a mixed hydride on the basis of its preparation. The mechanism of the reaction is not yet fully understood. The reducing species is presumably a mixture of zirconium borohydrides.

In summary, we believe that this procedure offers a simple and useful reduction of almost any kind of carbonyl compounds as well as imine derivatives and nitriles. Moreover, zirconium tetrachloride is inexpensive and easy to use. Further study on asymmetric reduction of ketones and oximes by use of this reagent is in progress.

Reduction with $ZrCl_4/NaBH_4$, 1-Phenylethanol; Typical Procedure:
$NaBH_4$ (1.51 g, 40 mmol) is added to a solution of $ZrCl_4$ (2.39 g, 10 mmol) in THF (35 mL) at room temperature under nitrogen. Immediate gas evolution is observed upon mixing the reagents, and a cream colored suspension is obtained. No black precipitate of zirconium borides is observed. A solution of acetophenone (0.93 mL, 8 mmol) in THF (10 mL) is added to the above mixture and is stirred for 5 h at room temperature. Then the reaction is quenched by the addition of water (20 mL) with ice-cooling and the mixture is then extracted with EtOAc (3 × 50 mL). In the case of oximes, imines, nitriles, and carboxamides the mixture is basified with 28 % aqueous ammonia to pH 9 and extracted with EtOAc (3 × 50 mL). The extract is washed with brine (80 mL), dried ($MgSO_4$), and evaporated. The crude product is purified by bulb-to-bulb distillation (Table).

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