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Reductive Cleavage of *N,N,N',N'*-Tetramethylphosphorodiamidates with Lithium Naphthalenide. A Convenient Procedure for Deoxygenation of Alcohols

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Abstract: A simple, effective alternative procedure has been developed for the reductive cleavage of the *N,N,N',N'*-tetramethylphosphorodiamidate group, using lithium naphthalenide as the reagent.

The reduction of a hydroxy group to the hydrocarbon level is a frequently encountered process in organic synthesis. A reliable method,[1] which also proved to be effective for sterically hindered alcohols,[2] involves the formation of a *N,N,N',N'*-tetramethylphosphorodiamidate (TMPDA) derivative[1,3] followed by reduction with lithium in liquid ammonia or ethylamine.[1] During the course of our synthetic studies of forskolin,[4] it was necessary to deoxygenate alcohol **1**. Thus, compound **1** was converted, using *N,N*-dimethylphosphoramidic dichloride and dimethylamine,[3] to the corresponding TMPDA **2** which was then subjected to reduction with lithium in ethylamine. The desired compound **3** was produced along with a minor amount of alcohol **1** resulting from the oxygen-phosphorus bond cleavage. However, there was considerable fluctuation in yield due to difficulties in duplicating the reaction conditions, especially in small scale preparation which requires the handling of a small quantity of the active metal and the low-boiling solvent, and the over-reduction resulting in the saturation of the carbon-carbon double bond. These problems were solved by the application of lithium naphthalenide (LN) as the reducing agent, which is stable and can be used in the form of a stock solution,[5] thereby allowing easy, more precise control of the experiment, and which does not effect the reduction of the carbon-carbon double bond. Treatment of **2** with LN gave consistently the desired product **3** in about 80% yield along with a small amount of alcohol **1** (~14% yield) via a procedure involving simply the addition of a stock solution of LN (4 eq) in tetrahydrofuran and allowing the reaction mixture to stand with stirring at room temperature for 30 min.

The effectiveness and generality of LN as a reagent for reductive cleavage of TMPDA's are evident from the results obtained for a number of compounds possessing an array of diverse functionalities. An examination of Table 1 reveals that the ketal (Entry 1), carbon-carbon double bond (Entries 1, 2, 4, 5, 7 and 8), hydroxy (Entry 4), silyl ether (Entry 5) and anisole (Entry 8) groups are all compatible to the reaction conditions applied. However, the unprotected ketone carbonyl could not survive under the reaction conditions.

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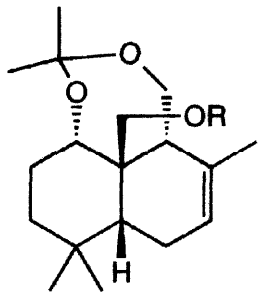
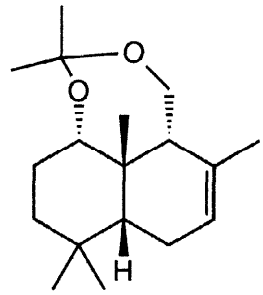


1 R = H

2 R = $P(O)(NMe_2)_2$



3

When the TMPDA derivative of 3ß-hydroxy-5-androsten-17-one (Entry 6) was treated with LN, a complex mixture was formed. The complication was apparently due to the susceptibility of ketone carbonyl to reduction, reductive coupling and addition reactions.[7] Attempts to circumvent this problem by prior formation of the enolate ion[8] using lithium diisopropylamide were also unsuccessful.[9] The use of potassium hydride as a base for the formation of the enolate ion (Entry 7) proved to be more successful, and 5-androsten-17-one was formed after LN reduction, albeit in low yield (27%). The current method was found to be equally effective for cleavage of the TMPDA derived from an enol. Thus, treatment of the TMPDA prepared from 3-methoxy-1,3,5(10)-trien-17-one (lithium diisopropylamide, *N,N,N',N'*-tetramethyldiamidophosphorochloridate, 25°C, 2 days)[1] with LN gave the corresponding olefin in 73% yield (Entry 8). This procedure may find general use to effect the overall transformation of ketones to alkenes.[1]

As described above, LN presents itself as a mild, effective reagent for the cleavage of the TMPDA group. In addition to good chemoselectivity, the application of this reagent has the great advantage of operational simplicity, as demonstrated by the following typical experiment.

A 0.66 M solution of LN in tetrahydrofuran (0.66 M, 2.4 mL, 1.6 mmol of LN) was added to 3ß-(*N,N,N',N'*-tetramethyldiamidophosphoroxy)-5-cholestene (196 mg, 0.38 mmol). The reaction mixture was stirred at room temperature under argon for 30 min. Water (10 mL) was added and the resulting mixture was extracted with ether (3 x 10 mL). The extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), filtered and concentrated. Flash chromatography of the residue on silica gel eluting with hexanes gave 5-cholestene (98 mg, 70% yield). Further elution with acetone-hexanes (1:3) gave cholesterol (44 mg, 17%).

Acknowledgment

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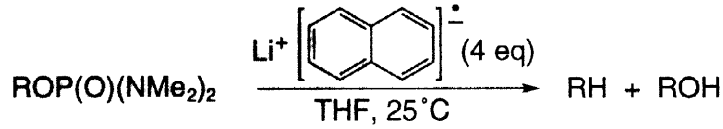
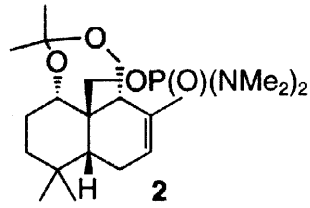
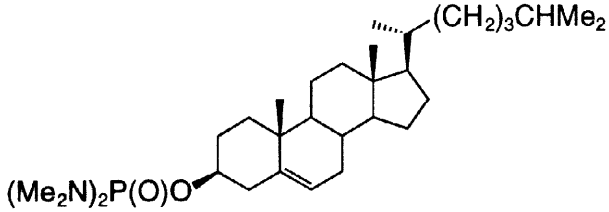
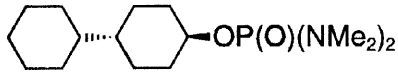
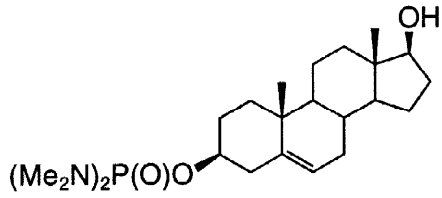
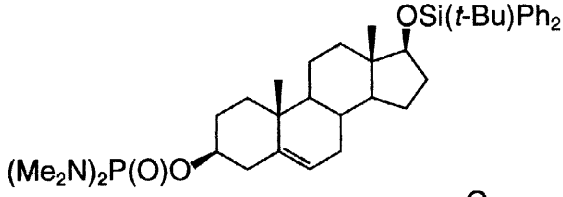
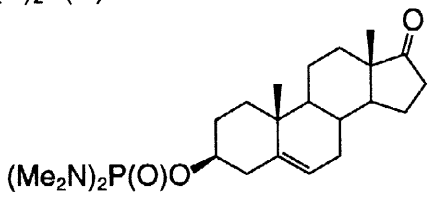
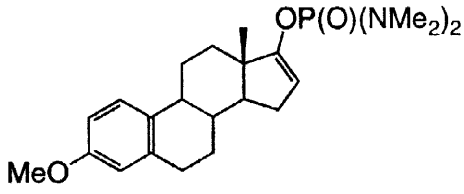
Table 1. Reductive Cleavage of *N,N,N',N'*-Tetramethylphosphorodiamidates with Lithium Naphthalenide



Entry	Substrate	Time (min)	% Yield[a] RH	% Yield[a] ROH
1		30	80	14
2		30	70	17
3		15	66	--
4		180	75	8
5		30	67	9
6		--	complex mixture	
7	" [b]	60	27	4
8		30	73	13[c]

[a] Yields are for isolated, chromatographically pure products. [b] The starting material was treated with an excess of potassium hydride at room temperature for 1 h prior to the addition of LN. [c] The corresponding ketone was formed.

References and Notes

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5. A 0.66 M stock solution of LN in tetrahydrofuran used in this work was easily prepared by addition of pieces of lithium metal (0.82 g, 0.12 mol) to a solution of naphthalene (16.6 g, 0.13 mol) in dry tetrahydrofuran (180 mL). The resulting mixture was stirred at room temperature under argon for 1 day, giving a dark blue solution. The stock solution was found to retain virtually the same reactivity after storage in a fridge at *ca.* -4°C under an argon atmosphere for more than a month. It is noteworthy that in most of the reported reduction reactions involving LN, an excess of lithium and a catalytic amount naphthalene were used.[6]
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9. A similarly produced lithium enolate was found to be stable to LN at -25°C.[8d] Unfortunately, at this temperature the reductive cleavage of TMPDA's was ineffective.