

A GENERAL METHOD FOR THE SELECTIVE REDUCTION OF KETONES IN THE PRESENCE OF ENONES.

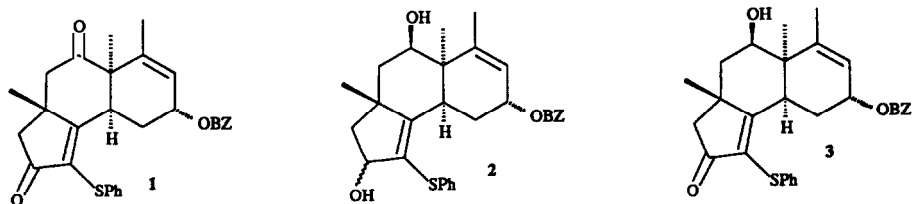
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Abstract: Ketones can be reduced in the presence of conjugated enones by sodium borohydride in 50% methanol in dichloromethane at -78°C . The selectivity is generally excellent. In favorable cases the reaction can be carried out at room temperature in dichloromethane with acetic acid as catalyst.

Sodium borohydride has been known as a mild and selective reducing agent in organic chemistry for over forty years¹. Aldehydes and ketones may be reduced to the corresponding alcohols in the presence of a wide variety of functional groups. Sodium borohydride is a so-called "nucleophilic" reagent in that the ease of reduction is related to the electrophilicity of the carbonyl group. The rate of reduction of an aldehyde can differ from that of a ketone by more than two orders of magnitude² (PhCHO vs. PhCOCH₃: 400x)³. This large difference in reduction rate can be exploited synthetically in that aldehydes can be reduced in the presence of ketones⁴. Similarly, α,β -unsaturated ketones are reduced more slowly than the corresponding ketones (cholestan-3-one vs. cholest-4-en-3-one: 7x)^{3,5}. Thus, under appropriate reaction conditions, it should be possible to reduce a ketone in the presence of a conjugated enone. While this type of selectivity has been demonstrated in specific cases⁶, to the best of our knowledge, a general method has not been reported.

In connection with a synthetic project, we observed a dramatic solvent effect in the reduction of the dione **1**⁷. Using excess sodium borohydride at room temperature, reaction in methanol provided a mixture of diols **2**. When 50% methanol in

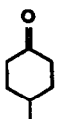
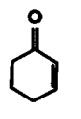

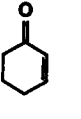
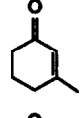
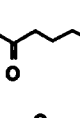
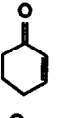
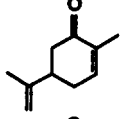

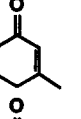
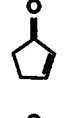
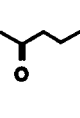
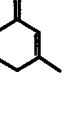
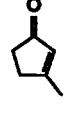
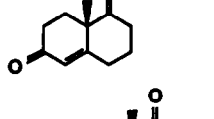
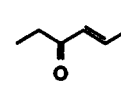
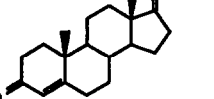


dichloromethane was used as solvent, in addition to **2**, the alcohol **3** was isolated (40% yield). Conducting the reaction at -78°C for 14 h gave **3** in quantitative yield.

We have investigated this process further and found it to be a general method for the selective reduction of ketones on the presence of conjugated enones. The results of several experiments are presented in Table 1 (method A). In each case the ketone is completely reduced (^1H NMR) while the enone remains largely intact (typically $>90\%$). The selectivity is poorest when a relatively reactive enone is in the presence of a relatively unreactive ketone. The reactivity of ketones can vary by more than two orders of magnitude⁸ (cyclohexanone vs. 2-hexanone: $300\times$)³. However, using longer reaction times, even unreactive ketones are reduced selectively in the presence of typical enones. It is noteworthy that these reductions are performed with excess borohydride and thus typical enones are stable under these conditions for many hours. The relative insensitivity of the selectivity towards both reaction time and reagent stoichiometry makes for an exceedingly simple protocol.

We were hopeful of achieving similar selectivity at room temperature by using the solvent composition to attenuate reactivity. Reducing the amount of methanol markedly reduces the rate of reduction, however we were unable to duplicate the selectivity observed above (using excess borohydride). At low methanol concentration ($<5\%$) reduction is quite slow. Addition of acetic acid dramatically catalyzes the reaction and reduction can occur at a rate faster than borohydride is decomposed⁹. Thus in dichloromethane alone no detectable reduction is observed; addition of excess acetic acid causes the rapid reduction of 4-methylcyclohexanone while enones remain largely intact. The results of several experiments are listed in Table 1 (method B). Selectivity is good with 4-methylcyclohexanone, however with less reactive ketones the reduction is incomplete. In favorable cases reactivity is enhanced without loss of selectivity by

Table 1

Starting ketones	Method ^a	%Reduction ^b		Starting Ketones	Method ^a	%Reduction ^b	
		Ketone	Enone ^c			Ketone	Enone ^c
 + 	A	>97	8(3)	 + 	A(14 h)	>97	40(3)
	B	>97	13(2)		B	40	12(2)
	B(5%MeOH)	67	43(2)		B(5%MeOH)	67	43(2)
" + 	A	>97	<3(>10)	 + 	A(14 h)	>97	42(3)
	B	>97	9(>10)		B	32	15(2)
	B(5%MeOH)	54	45(2)		B(5%MeOH)	54	45(2)
" + 	A	>97	4(3)	 + 	A(14 h)	>97	4(>10)
	B	>97	15(3)		B(5%MeOH)	>97	7(>10)
" + 	A	>97	<3(.5)	 + 	A(14 h)	>97	5(>10)
	B	>97	4(2)		B(5%MeOH)	>97	11(>10)
" + 	A	>97	<3(?)		A	>97	<3(>10)
	B	>97	<3(>10)		B	38	6(>10)
	B(5%MeOH)	>97	8(>10)		B(5%MeOH)	>97	8(>10)
" + 	A	>97	4(>10)		A(6 h)	>97	7(>10)
	B	>97	5(>10)		B	13	13(>10)

a; 50 μ l of each ketone, 50 mg of sodium borohydride, in 5 ml of solvent, or 20 mg of dione, 20 mg sodium borohydride, in 5ml of solvent; b: by NMR; c: the value in parenthesis is the ratio of 1,2 to 1,4 reduction.

the addition of up to 5% of methanol. The use of higher methanol concentrations, while causing complete reduction of the ketone, results in much lower selectivity¹⁰.

General Procedure A: a solution of the Wieland-Miescher ketone (21 mg) in 50% methanol in dichloromethane (5 ml) was cooled in a dry ice-acetone bath and sodium borohydride (20 mg) was added. After stirring for 1 h, acetone (1 ml) was added and the reaction was allowed to warm to room temperature. The mixture was diluted with dichloromethane, washed with 1M NaOH, dried over Na_2SO_4 and concentrated to give the 1- β -alcohol (21 mg) which was contaminated by less than 3% (¹H NMR) of the corresponding diol.

General Procedure B: A solution of the Wieland-Miescher ketone (20 mg) was dissolved in dichloromethane (5 ml) containing 5% of methanol and sodium borohydride (22 mg) was added. The resulting suspension was stirred vigorously and acetic acid (280 mg) in 5% methanolic dichloromethane (1 ml) was added (**CAUTION:** H₂ evolution). After 10 min the reaction mixture was diluted with dichloromethane, washed with 1M NaOH, dried over Na₂SO₄ and concentrated to give the 1-β-alcohol which was contaminated by 8% (¹H NMR) of the corresponding diol.

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