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DEPROTONATIONS, CONJUGATE ADDITIONS, AND ENOLATE TRAPPING OF OXIME ETHERS AND DIMETHYLHYDRAZONES USING KDA. THE EFFECT OF DIISOPROPYLAMINE ON ENOLATE TRAPPING.

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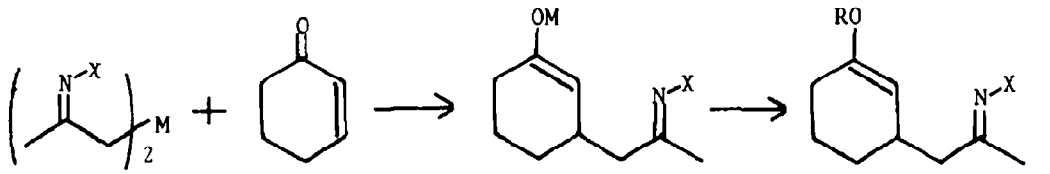
Abstract: Potassium diisopropylamide (KDA) has been used to efficiently generate the anions of oxime ethers and dimethylhydrazones. As a deprotonating agent, KDA is superior to BuLi and LDA. The corresponding cuprates are extremely oxygen sensitive, but undergo 1,4-addition with cyclohexenone, and the resulting potassium enolates can be trapped with aqueous buffer or $ClSiMe_3$. Attempted trapping with either Ac_2O or AcCl in the presence of diisopropylamine fails.

The alkylation of oxime ethers[1] and dimethylhydrazones[2] has received considerable attention from synthetic chemists recently. For our own program investigating reactions involving heterolysis of N–X bonds, we required a general route to compounds having the general structure indicated by 3, where $X=NMe_3^+$; OMe; OTs, and OH. The recent report by Corey and Enders[2f] indicating that dimethylhydrazone cuprates suffer conjugate addition when treated with α,β-unsaturated ketones suggested the solution illustrated below, provided that: (i) The copper would not chelate the enolate and imine thus preventing or deterring trapping; and (ii) Oxime ethers would form cuprates and undergo 1,4-addition to enones.

For our own efforts at alkylating oxime ethers and dimethylhydrazones, we have found potassium diisopropylamide (KDA)[3] to be a more reliable base than either n-butyllithium or lithium diisopropylamide (LDA). Usually, one or the other of the latter bases is used to deprotonate oxime ethers or dimethylhydrazones. The base of choice sometimes depends on the structure of the particular imine, and it is thus considerably more convenient to have one base available to routinely do the job. KDA will quantitatively deprotonate most dimethylhydrazones and oxime ethers (O-methyl and O-tetrahydropyranyl), derived from cyclic and acyclic ketones, in THF at -78° in 15 minutes or less.

In contrast, dimethylhydrazones of methyl ketones are deprotonated in 20 minutes in THF solution using LDA at 0° or n-butyllithium at -78°, while cyclic ketones sometimes require lengthy reaction times for deprotonation. 2-Methylcyclohexanone dimethylhydrazone, for example, requires treatment for 20 hours with LDA at 0° to accomplish deprotonation.[2e,2i] 30 minutes are required for the same dimethylhydrazone with KDA at -78°. Parenthetically, 4-t-butylcyclo-



1

a: X = NMe_2

b: X = OMe

2

a: M = K, X = NMe_2

b: M = Li, X = NMe_2

c: M = K, X = OMe

d: M = Li, X = OMe

3

a: R = H, X = NMe_2

b: R = Ac, X = NMe_2

c: R = Me_3Si, X = NM

d: R = H, X = OMe

e: R = Ac, X = OMe

f: R = Me_3Si, X = O

hexanone dimethylhydrazone is alleged to deprotonate in 2 hours with LDA at 0°[2e], contradic an earlier report from the same group which indicated a 20 hour reaction time requiremen

Literature procedures for the deprotonation of O-methyl oximes with LDA[1a] indicate a 1 reaction time at -78° in THF containing 4% HMPA.[4] In our hands, this has not been a reli procedure, presumably due to difficulties encountered in thoroughly drying the HMPA. O-Te hydropyranyl oximes reportedly require up to 3 hours reaction with LDA in THF to ach deprotonation.[1c]

Following deprotonation, cuprate formation proceeds routinely, however we have found more convenient to use House's cuprous bromide-methyl sulfide complex[5] in place of the cup iodide-isopropyl sulfide complex used by Corey and Enders[2f]. The presence of a potas counterion has no deleterious effect on either cuprate formation or conjugate addition. Tab shows that the yield for the conjugate addition of the acetone dimethylhydrazone cuprate(methyl sulfide complex is comparable to the reported yield, and also reports the yield for conjugate addition of the cuprate of acetone O-methyl oxime (1b). O-Tetrahydropyranyl ox also form cuprates and undergo 1, 4-addition to cyclohexenone under similar conditi Quenching of the enolates 2a-d with NH_4Cl buffer (pH 8) produced the ketones 3a and 3d in ne quantitative yield. The trapping of the lithium or potassium enolates 2a-d with chl trimethylsilane proceeded routinely to afford enol ethers 3c and 3f in excellent yield.

Attempted trapping of O-methyl oxime potassium enolate 2c with either acetic anhydrid acetyl chloride was unsuccessful. None of the ketone 3d or any product of acylation of eno 2c or O-methyl acetone oxime could be found in the reaction mixture. The only product which not codistill with the solvent during workup was diisopropylacetamide.

As a control experiment, potassium enolate 2c was prepared and divided into two porti the first was quenched with ammonium chloride solution to produce ketone 3d, and the second quenched with acetyl chloride, which produced diisopropylacetamide. Thus, enolate 2c decomposing on addition of acetyl chloride. The lithium enolate 2d was generated from trimethylsilyl enol ether using methyl lithium[6] and quenched with acetyl chloride to produce enol acetate oxime ether 3e in 95% yield.

TABLE I. YIELD DATA FOR THE PREPARATION OF 3.

	R	X	YIELD, % Crude	Distilled
3a	H	NMe_2	95[a,b,c]	75[c]
3b	Ac	NMe_2	88[a,d]	43
3c	Me_3Si	NMe_2	92[a]	58
3d	H	OMe	98[e,b]	92
3e	Ac	OMe	95[f]	47
3f	Me_3Si	OMe	78[e]	47

(a) DMH anion generated with n-butyllithium. The yields for 3a and 3c are comparable if KDA is used. (b) Enolate quenched with NH_4Cl buffer (pH 8). (c) Literature yield of crude product = 96%, no distilled yield reported (ref.2f). (d) Enolate quenched with acetic anhydride. (e) Oxime ether anion generated with KDA. (f) Lithium enolate generated from silyl enol ether with methyllithium and quenched with acetyl chloride.

To test whether or not this phenomenon was limited to the oxime ether derivatives, the potassium cuprate 1a was converted to enolate 2a, which was divided into three portions. The first was quenched with ammonium chloride to produce 3a; the second was quenched with chlorotrimethylsilane to produce 3c; and the third was quenched with acetyl chloride, to produce diisopropylacetamide. Since no trace of 3a or any other nonvolatile component was detected, we conclude that enolate 2a is also decomposed upon attempted acylation.

Since lithium enolate 2d could be easily acylated while potassium enolate 2c could not, the anomaly must be attributable either to the presence of the potassium counterion, or to the lithium t-butoxide, or to the diisopropylamine which were also present with 2c as byproducts from the preparation of KDA.

To identify the culprit, lithium enolate 2d was generated from the enol silyl ether 3f and treated with 1 equivalent of lithium t-butoxide followed by acetyl chloride to produce enol acetate 3e. However, when enolate 2d was treated with excess acetyl chloride in the presence of 1 equivalent of diisopropylamine, diisopropylacetamide was the only nonvolatile product found. In particular, no ketone (3d) or any higher molecular weight acylation product of 2d could be found. Control experiments indicate that 3d and 3e would be easily detectable in a mixture with diisopropylacetamide. From the absence of 3d, we can conclude that the problem is not an acid-base reaction between the enolate and the acetyl chloride. The fact that the products of the enolates decomposition codistill with THF suggests that the enolate is being cleaved in some way. We suggest a retrograde Michael reaction as being the most reasonable mode.

A final comment should be made regarding what we consider to be rather painstaking, albeit necessary experimental precautions. Our initial attempts at duplicating Corey's procedure for the synthesis of 3a produced mixed results. The problem was eventually traced to oxygen quenching of the cuprate, and the extreme sensitivity of these cuprates to oxygen bears some mention. Oven-dried glassware, argon atmosphere, and scrupulously dried solvent failed to

eliminate the source of the culprit oxygen. The precaution which finally solved the problem transfer of solvent and reagents by cannulation or gas-tight syringe. Experimental details the preparation of 3f are provided as a typical procedure[7]. KDA was prepared by adding 2.00 of a 1.6 M solution of n-butyllithium (3.2 mMol) to a cold (-78°) slurry of 0.36 g potass t-butoxide (3.2 mMol) and 0.32 g of diisopropylamine (3.2 mMol) under an atmosphere of dry ar in 35 ml of dry THF (distilled from sodium benzophenone ketyl). A solution of 250 mg of acet O-methyl oxime (2.9 mMol) was added dropwise to the cold (-78°) solution of KDA. After stirr for 15 min, a precooled (-30°,CO_2/PhBr) solution containing 0.23g of cuprous bromide (1.6 mM and 15 ml methyl sulfide in 15 ml of dry THF was added dropwise via double ended needle. reaction mixture was warmed to 0°C over the course of 1 h to form a homogeneous yellow cupr solution, then recooled to -78°C. Cyclohexenone (0.16 mL, 1.6 mMol) was added and the react was stirred for 15 h, gradually warming to room temperature. The light brown suspension quenched with 3 mL(23.6mMol) of chlorotrimethylsilane and stirred for 30 min. The reaction partitioned between saturated NH_4Cl buffer (pH 8) and CH_2Cl_2. The organic layer was washed w buffer until no blue color remained. The combined aqueous layers were extracted once w CH_2Cl_2 and the combined organic layers were diluted with ether, washed with saturated NaHC dried with $MgSO_4$ and condensed to a light yellow oil (0.32g). Kugelrohr distillation from K_2 provided 0.19g (47%).

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