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TRIS(PHENYLTHIO)METHYLLITHIUM AS A FORMYL ANION EQUIVALENT IN CONJUGATE ADDITION. PREPARATION OF UNPROTECTED γ-KETOALDEHYDES.

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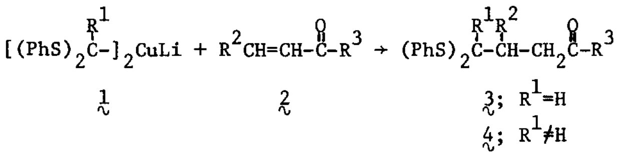
Despite the plethora of available acyl anion equivalents,[1] there are apparently no known procedures for converting an enone into a 4-ketoaldehyde by β-addition of a formyl anion equivalent followed by unmasking to an aldehyde group. The products constitute an important class of compounds; of particular current interest is the conversion to cyclopentenones which can serve as precursors of jasmonoids, rethrolenoids, and prostaglandins.[2] Most of the potential methods suffer from either of the following problems: 1) The anion adds 1,2 rather than 1,4. 2) The conditions required for the unmasking are destructive to the highly sensitive[3] products. For example, the familiar thioacetal anions exhibit a high selectivity for 1,2-addition;[1b] on the other hand, cyanide ion adds mainly 1,4 but the reduction required for the conversion of the nitrile to an aldehyde function (diisobutylaluminum hydride has been used[4]) reduces the ketone to an alcohol. The most nearly successful procedures have involved the base-catalyzed addition of nitromethane to an enone,[5] protection of the ketone function as an acetal, and conversion of the CH_2NO_2 group to CHO by either an oxidative method[6a] (the yield was unspecified), a modified Nef reaction utilizing sodium methoxide adsorbed on silica gel (81% yield),[6b] or a reductive method utilizing $TiCl_3$(90% yield);[6c] in none of these cases were the products hydrolyzed to 4-ketoaldehydes.[7]

In connection with our work on the development of a new mild furan synthesis,[8] we sought a fairly general preparation of the 4-ketothioacetals **3**. Mukaiyama[9] had reported the valuable observation that cuprates (**1**) of thioacetals add in conjugate fashion to enones (**2**) (eq. 1) and this has been verified in our laboratory.[8,10] However, when the thioacetal involved is that of formaldehyde, no adduct **3** could be isolated.[10,11]

(1)

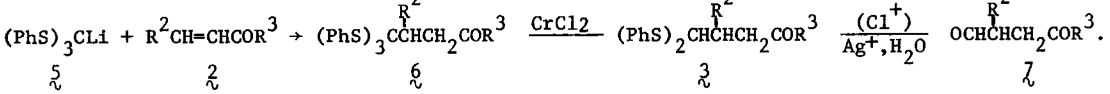


$$[(PhS)_2\overset{R^1}{C}-]_2CuLi + R^2CH{=}CH-\overset{O}{\overset{\|}{C}}-R^3 \rightarrow (PhS)_2\overset{R^1}{C}-\overset{R^2}{C}H-CH_2\overset{O}{\overset{\|}{C}}-R^3$$

$$\underset{\sim}{1} \qquad \underset{\sim}{2} \qquad \underset{\sim}{3};\ R^1{=}H \qquad \underset{\sim}{4};\ R^1{\neq}H$$

Manas and Smith[12] have observed that the readily prepared[13] tris(phenylthio)methyllithium (5) adds in conjugate fashion to a number of enones 2 (Scheme I).[14] We reasoned that replacement of a single phenylthio group of the adducts (6) with hydrogen by a reaction proceeding via an intermediate radical should be successful in view of the expectation that two phenylthio groups should stabilize a radical[15] far more effectively than a single phenylthio group; thus, under the mildest reduction conditions which would accomplish the purpose, the product (3) should not be further reduced. Not surprisingly in retrospect, a heterogeneous system (Raney nickel), utilized for reduction of the model compound tris(phenylthio)methane, was not sufficiently selective with regard to a single-stage desulfurization, presumably because the adsorption process rivaled or surpassed the stability of the radical intermediate as a determinant of rate. By using a homogeneous system, however, it was shown that the concept is indeed sound. Since chromium(II) ions are known to cause the replacement of halogen by hydrogen,[16] it seemed reasonable to expect a phenylthio group to be similarly displaceable. It was found that the yields of 1-stage reduction product were uniformly excellent (Table I)[17] when 6 equivalents of $CrCl_2$ were used per mole of substrate in DMF-water at 100° for 3 hours.[18] (Scheme I).

SCHEME I



$$(PhS)_3CLi + R^2CH{=}CHCOR^3 \rightarrow (PhS)_3C\overset{R^2}{C}HCH_2COR^3 \xrightarrow{CrCl2} (PhS)_2CH\overset{R^2}{C}HCH_2COR^3 \xrightarrow[Ag^+,H_2O]{(Cl^+)} OCH\overset{R^2}{C}HCH_2COR^3.$$

$$\underset{\sim}{5} \qquad \underset{\sim}{2} \qquad \underset{\sim}{6} \qquad \underset{\sim}{3} \qquad \underset{\sim}{7}$$

Table I. 6 → 3

R^2	R^3	Yield (%)	Mp 3, °C
Ph	Ph	94	83.5-84.0
Ph	Me	99	oil
Me	Ph	97	oil
$-CH_2CH_2CH_2-$		99	52.5-53.5
$-CH_2CH_2-$		95	47.5-48.0

Table II. 3 → 7

R^2	R^3	Yield (%)
Ph	Ph	90
Ph	Me	85
Me	Ph	82
$-CH_2CH_2CH_2-$		70
$-CH_2CH_2-$		45

The hydrolysis of a thioacetal $RCH(SR^1)_2$ in which R is a saturated alkyl group is frequently a difficult task[1b] and is a particularly delicate one here because of the instability of the product. We finally adopted a modification of Corey's N-chlorosuccinimide procedure[19] in which the substrate was treated with trichloroisocyanuric acid (Chloreal)[20] and silver nitrate in acetonitrile-water (4:1) containing suspended cadmium carbonate. The yields are in Table II.[21]

Typical procedures for the reduction and hydrolysis follow. Reduction: A solution of 8.85 g (72.0 mmol) of chromous chloride and 6.57 g (12.0 mmol) of 1,3-diphenyl-4,4,4-tris-(phenylthio)-1-butanone[12] (6; $R^2 = R^3 = Ph$) in degassed dimethylformamide (120 ml)-water (12 ml) was heated at 100°C for 3 hr. under argon. The cooled solution was added to 500 ml of water and the cloudy suspension was extracted with ether (3 x 50 ml). The extract was washed with 2 N NaOH, 2 N HCl, sat'd aq. $NaHCO_3$, distilled water and brine; it was dried ($MgSO_4$), and evaporated to yield an oil which, upon trituration with hexane, yielded 4.96 g (94%) of spectroscopically (^1H NMR) pure 1,3-diphenyl-4,4-bis(phenylthio)-1-butanone (3; $R^2 = R^3 = Ph$; mp 83.5-84.0, after recrystallization from ethanol). Hydrolysis: A solution of 310 mg (0.70 mmol) of this product in 2 ml of acetonitrile was added rapidly by addition funnel to a vigorously stirred suspension of 280 mg (1.2 mmol) of Chloreal, 730 mg (4.3 mmol) of $AgNO_3$, and 360 mg (2.1 mmol) of $CaCO_3$ in 20 ml of acetonitrile-water (4:1). The mixture was stirred for 20 min., filtered through Celite, and washed through with ether. The aqueous layer was removed and the organic layer washed with sat'd aq. KI, sat'd aq. $Na_2S_2O_3$, water, and brine. Evaporation of the dried (Na_2SO_4) organic layer yielded a yellow oil which, upon silica chromatography using $CHCl_3$ for elution, gave 150 mg (90%) of the ketoaldehyde 7 ($R^1 = R^3 = Ph$).

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7. A less successful method for the preparation of the same protected compound involves the conjugate addition of phthalimidonitromethane to an unhindered enone and conversion in three steps to a 4-formylketal (45% yield).[3] An attempt to prepare the unprotected 4-ketoaldehyde by the same unmasking procedure failed completely.[3]

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14. In the addition to **2** (R^2=Ph; R^3=Me) we obtained only a 40% yield as opposed to the 60% reported.[12] The addition to cyclopentenone was also successful (95% yield). On the other hand, no adduct could be obtained with cinnamaldehyde and 1-acetylcyclohexene.

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17. Satisfactory ^{1}H NMR, mass and IR spectral data were obtained for all new compounds. In addition, satisfactory combustion analyses were obtained for all stable compounds. For the more unstable of the ketoaldehydes, exact masses or combusion analyses of the corresponding N-phenyl pyrroles, formed by condensation with aniline, were obtained.

18. Substitution of perchlorate, tetrafluoroborate or acetate for chloride, or the use of a lower ratio of $CrCl_2$ to substrate led to inferior yields; use of ethanol or acetonitrile (reflux) as solvent gave no **3**.

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21. Another promising method[10] for the production of **3** consisted of the addition of **1** [R^1=Si(Me)$_3$] to **2** followed by the clean replacement of Si(Me)$_3$ in **4** [R^1=Si(Me)$_3$] by H by the use of KF·2 H_2O. Excellent yields were obtained in a number of experiments but, unfortunately, the results were not always reproducible.

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