

A NOVEL CARBONYL ANION EQUIVALENT AND ITS APPLICATION
TO THE SYNTHESIS OF ALDEHYDES AND KETONES

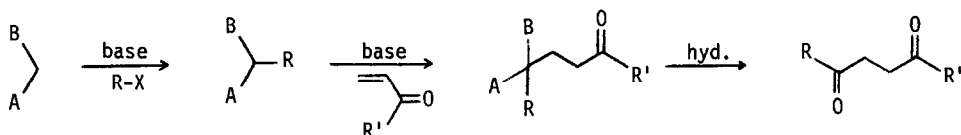
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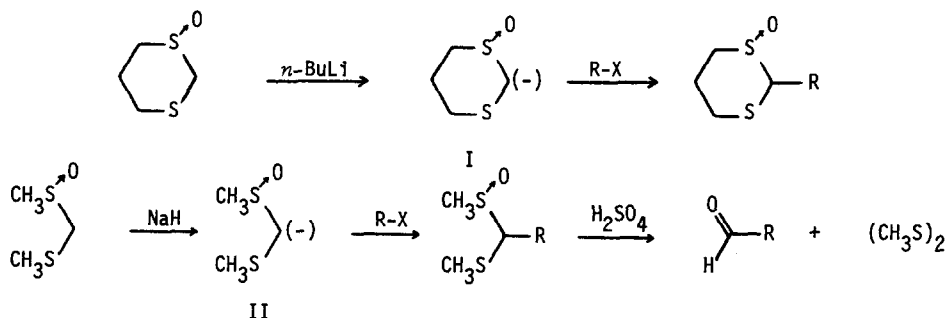
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For some time we have felt that it would be highly desirable to devise a synthetic method which would permit an efficient "linch-pin" construction of unsymmetrically substituted 1,4-dicarbonyl compounds.¹ In principal, this novel strategy (outlined below) could be accomplished using a carbonyl anion equivalent which possesses the chemical versatility to undergo both alkylation and conjugate addition.² Carbonyl anion equivalents thus far devised either alkylate



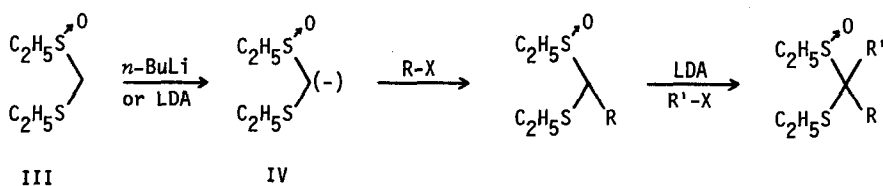
but do not conjugatively add (dithianes)³ or else they conjugatively add but do not alkylate (nitro compounds).⁴ In this communication we will outline the alkylation chemistry of a new class of carbonyl anion equivalents. The accompanying communications describe the conjugate addition behavior of these species and their application to the efficient construction of 1,4-dicarbonyl compounds.

In searching for an appropriate carbonyl anion equivalent, our attention was attracted to the anions I⁵ and II.⁶ Both anions were reported to alkylate, and the alkylation products of II were found to hydrolyze with sulfuric acid into the corresponding aldehyde and methyl disulfide.⁶ Conjugate addition reactions of I and II were not reported, however.



We have reexamined the alkylation reactions described for both I and II and have found that neither system, as described, constitutes a satisfactory synthetic method for preparing aldehydes or ketones. For example, two very low yield reactions were reported for I, methylation and benzylation.⁵ Even after considerable modification, we have realized only slightly improved yields for these reactions. On the other hand, several good to high yield alkylation reactions have been reported for the anion II.⁶ However, we have been able to obtain only modest alkylation yields with II using the reported reaction conditions and then only in the presence of a five to ten fold excess of the alkylating agent. Furthermore, dialkylation could not be achieved with either anion, thus negating the preparation of ketones by this method.

After some experimentation, we have found that the most convenient thioacetal monosulfoxide of this type to use is the diethyl compound III.⁷ Sulfoxide III, when treated with one equivalent of either n -butyllithium or lithium diisopropylamide (LDA) at 2° in THF solution, quantitatively yields the anion IV within thirty minutes.⁸ One molar solutions of this anion when al-



lowed to react with alkylating agents (1.0 to 1.5 equivalents) at 25° (2 to 10 hours) undergo monoalkylation in greater than 95% yield.⁹ A second alkylation step is also possible using the same experimental conditions and these reactions proceed in greater than 90% yield.¹⁰ A summary of some typical results are given in the table. The stoichiometric requirements with respect to the alkylating agent are noted in parentheses for each reaction.

TABLE

Sulfoxide	Alkylating Agent	R	Product
$C_2H_5SCH_2SOC_2H_5$	CH_3CH_2I (1.1)	CH_3CH_2-	$C_2H_5SCH(R)SOC_2H_5$
$C_2H_5SCH_2SOC_2H_5$	$CH_3CH_2CH_2I$ (1.1)	$CH_3CH_2CH_2-$	$C_2H_5SCH(R)SOC_2H_5$
$C_2H_5SCH_2SOC_2H_5$	$CH_3CH_2CH_2CH_2Br$ (1.5)	$CH_3CH_2CH_2CH_2-$	$C_2H_5SCH(R)SOC_2H_5$
$C_2H_5SCH_2SOC_2H_5$	$(CH_3)_2CHBr$ (1.1)	$(CH_3)_2CH-$	$C_2H_5SCH(R)SOC_2H_5$
$C_2H_5SCH_2SOC_2H_5$	$Br(CH_2)_3Br$ (1.3)	$Br(CH_2)_3-$	$C_2H_5SCH(R)SOC_2H_5$
$C_2H_5SCH_2SOC_2H_5$	$CH_2=CHCH_2Br$ (1.1)	$CH_2=CHCH_2-$	$C_2H_5SCH(R)SOC_2H_5$
$C_2H_5SCH(C_2H_5)SOC_2H_5$	$CH_3CH_2CH_2I$ (1.1)	$CH_3CH_2CH_2-$	$C_2H_5SC(C_2H_5)(R)SOC_2H_5$
$C_2H_5SCH(C_2H_5)SOC_2H_5$	$CH_3CH_2CH_2CH_2Br$ (1.1)	$CH_3CH_2CH_2CH_2-$	$C_2H_5SC(C_2H_5)(R)SOC_2H_5$
$C_2H_5SCH(C_2H_5)SOC_2H_5$	$Br(CH_2)_3Br$ (1.5)	$Br(CH_2)_3-$	$C_2H_5SC(C_2H_5)(R)SOC_2H_5$
$C_2H_5SCH(C_2H_5)SOC_2H_5$	$CH_2=CHCH_2Br$ (1.1)	$CH_2=CHCH_2-$	$C_2H_5SC(C_2H_5)(R)SOC_2H_5$

We have also experienced difficulties hydrolyzing the above sulfoxides with sulfuric acid,⁶ particularly in those cases which lead to aldehyde products.¹¹ This problem is easily circumvented by treating the sulfoxides (1 equivalent, 0.5 molar in ether) with a catalytic amount of 70% perchloric acid (4°, 20 minutes). These reaction conditions lead to the quantitative formation of the desired carbonyl compound along with ethyl disulfide. The latter substance presents serious difficulties with respect to the purification of aldehydes or ketones which have boiling points below 220° (1 torr).¹² However, formation of the disulfide component can be completely eliminated by hydrolyzing the sulfoxide in the presence of a mercuric salt. Typically, the sulfoxide (1 equivalent), dissolved in a minimum amount of THF, is added to mercuric chloride (4 equivalents) suspended in a 4:1 (by volume) mixture of THF and 9 N hydrochloric acid. The resulting mixture (0.5 molar in sulfoxide), after stirring for 1.5 hours at 0°, gives rise to aldehyde or ketone (80 to 95% yield) uncontaminated with the disulfide.

In summary, alkylation of the carbonyl anion equivalent III, as described herein, is applicable to the viable synthesis of a variety of aldehydes and ketones. These reactions are convenient to carry out on both a small and large scale, and furthermore, they are compatible with reasonable stoichiometry.

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REFERENCES

- 1,4-Dicarbonyl compounds are useful synthons for further transformations into either furan or cyclopentenone systems (for examples, see reference 4 and references cited therein).
- This type of construction using a sulfur stabilized carbonyl anion equivalent has recently been realized by T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Amer. Chem. Soc.*, **94**, 8641 (1972). In this case the conjugate addition step was carried out *via* an organo copper intermediate.
- For an extensive review of 1,3-dithiane chemistry, see D. Seebach, *Synthesis*, **1**, 17 (1969).
- For an elegant use of nitro alkanes in the construction of 1,4-dicarbonyl systems, see J. E. McMurry and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (1971).
- R. M. Carlson and P. M. Helquist, *J. Org. Chem.*, **33**, 2596 (1968).
- K. Ogura and G. Tsuchihashi, *Tetrahedron Letts.*, 3151 (1971).
- Compound III was prepared from methylal and ethyl mercaptan followed by meta-periodate oxidation of the intermediate thioacetal. The overall yield of III (bp 90°, 5 x 10⁻³ torr) from methylal is 90%. Another preparation of III has been reported by K. Ogura and G. Tsuchihashi, *Bull. Chem. Soc., (Japan)* **45**, 2203 (1972).
- The extent of anion formation was determined by quenching with D₂O. Anion IV is quite stable for prolonged periods of time even at elevated temperatures.
- Monoalkylated sulfoxides derived from III are readily distillable materials. The yields given are for isolated products and are based on the amount of III used. All compounds exhibited satisfactory spectral and physical properties.
- Dialkylated sulfoxides are usually not purified, but rather converted directly into their corresponding ketones. Thus, the yields given are for the ketone obtained (based on sulfoxide used) and represent a minimum yield for the alkylation step.
- Aldehyde self-condensation appears to be the major side reaction under these reaction conditions.
- Both ethyl and methyl disulfide azeotrope with almost any ketone or aldehyde boiling below 220° (1 torr), thus necessitating isolation of the carbonyl product *via* a higher boiling or crystalline derivative as done in reference 6.