CONJUGATE (1,4) ADDITION OF HETEROCYCLIC ACYL ANION EQUIVALENTS TO CYCLIC α-ENONES IN THE PRESENCE OF HEXAMETHYLPHOSPHORIC TRIAMIDE: A GENERAL REACTION[1]

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ABSTRACT - Heterocyclic dithiaorganolithium reagents react with cyclic α-enones in THF to yield only products of carbonyl (1,2) addition; in the presence of 2.0 equivalents of hexamethylphosphoric triamide, the addition proceeds to give nearly exclusively the products of conjugate (1,4) addition in good yield.

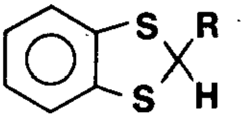
Conjugate addition of α,α-dithiaorganolithium reagents to α-enones has been sought as a route to synthetically important 1,4-dicarbonyl systems.[2]

$$(ZS)_2CRLi + O{=}C{-}C{=}C \rightarrow O{=}C{-}C{-}C{-}CR(SZ)_2 \rightarrow O{=}C{-}C{-}C{-}C{=}O$$

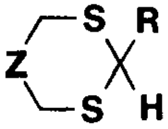
Unfortunately, such systems in which the carbanion is not further activated (e.g. by aryl[3]) have been observed to yield products of carbonyl attack.

Recently we[4] and others[5] have independently reported that 2-lithio-1,3-dithianes - which react with cyclic α-enones exclusively by carbonyl addition - can be induced to undergo conjugate additions by the addition of at least 1.0 equivalent of hexamethylphosphoric triamide (HMPTA). This method has been employed by Thomas and Heathcock in a novel annelation sequence.[6]

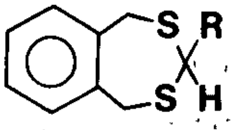
We now report that conjugate addition to cyclic α-enones induced by HMPTA is a general reaction of anions of cyclic dithiaheterocycles, including systems with five, six, and seven membered rings as well as additional heteroatoms; examples are shown below.



I



IIa $Z{=}CH_2$
IIb $Z{=}S$
IIc $Z{=}NCH_3$



III

Carbanions were generated by published procedures, using n-BuLi in THF-hexane.[7] Treatment of the anions with 2.5M 2-cyclohexen-1-one in 1:1 hexane-THF, dropwise at -80°, followed by hydrolysis after one hour with methanol and then saturated aqueous NH_4Cl yielded only the carbonyl addition products. However, addition of HMPTA to the anion solution, followed by stirring for 30-60 min. at -80°, addition of cyclohexenone, and workup[8] yielded products of conjugate addition. Addition of HMPTA to solutions of the anionic products of carbonyl addition (Va) produced no rearrangement to IVa, even after warming to room temperature, as shown in the scheme below. The results of the conjugate addition experiments with I, II, and III (R = H, CH_3, $(CH_3)_3Si$) are shown in the Table.

SCHEME

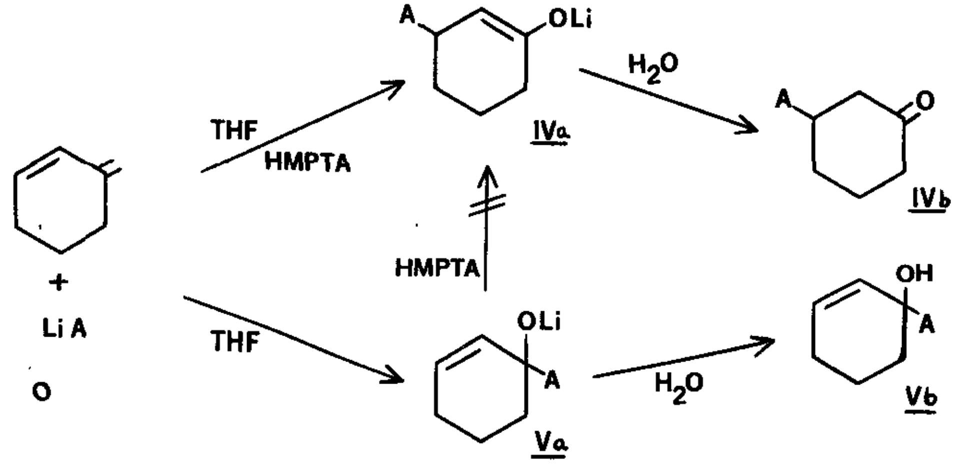


TABLE: Conjugate Addition in the Presence of HMPTA

Anion From	Ketone	Yield,%[b]	1,4/1,2[c]
I R=H	cyclohexenone	79	81:19
I R=Me	cyclohexenone	81	93:7
IIa R=H	cyclohexenone	77-87	92:8
IIa R=H	cyclopentenone	84	96:4
IIa R=H	cycloheptenone	69	72:28
IIa R=H	3-me-c'hexenone	55	10:90
IIa R=H	5,5-dime-c'hexenone	79	93:7
IIa R=Me	cyclohexenone	82	96:4
IIa R=Me_3Si	cyclohexenone	82	96:4
IIb R=H	cyclohexenone	75	94:6
IIc R=H	cyclohexenone	73	93:7
III R=H	cyclohexenone	69[d]	96:4
$CH_3SCH_2SCH_3$	cyclohexenone	77	94:6

[a] 2.5mmole anion, 5.0 mmol HMPTA, 2.5mmol ketone, -80°, 10ml 3:1 THF:hexane.

[b] Isolated, distilled yield of isomer mixture.

[c] By glpc analysis of sample of reaction mixture before distillation. Analyses essentially the same after distillation. Approx. 5-15% starting material observed in glpc analyses before distillation.

[d] Chromatographed yield.

The products of IVb contained minor amounts of Vb[9], which proved laborious to separate chromatographically, especially when R=H. However, treatment of (CCl_4, 60°, 2-3 hrs)of the crude products with N-trimethylsilyl imidizole followed by chromatography (SiO_2, 20-30% ethyl acetate/hexane) allowed facile separation.

Conjugate addition of IIa to cyclopentenone and cycloheptenone have been described earlier.[4] Preliminary results indicate that these, as well as various methylated cyclohexenones, react similarly with anions of I-III; however, 3-methylcyclohexenone and 4,4-dimethylcyclohexenone yield mainly carbonyl addition products, even in the presence of HMPTA, presumably for steric reasons. Although beyond the general scope of this study, some acyclic dithiacarbanions were also examined and found to behave similarly. Thus anions of ZSCHRSZ (R=H, CH_3, C_2H_5, Z=CH_3, C_6H_5) were found to undergo conjugate addition to cyclohexenone and cyclopentenone in the presence of HMPTA.

These observations establish the use of HMPTA-coordination as a valuable technique for affecting the mode of addition of heterocyclic acyl anion equivalents to enones; however, elucidation of the mechanism by which such coordination is effective (chelating diamines are completely ineffective) awaits further work.

REFERENCES AND NOTES

1. Dedicated to Professor Herbert C. Brown on the occasion of his 70th birthday. One of us (C.A.B.) owes special gratitude to Professor Brown as his father as well as for an early introduction to chemical research.

2. For general references on this topic, see the references in ref. 4 and ref. 5.

3. For some examples of conjugate addition to enones by activated dithianes, see P.C. Ostrowski and V.V. Kane, Tetrahedron Lett., 1977, 3549; F.E. Ziegler and C.C. Tam, Tetrahedron Lett., 1979, 4717; B.-T. Grobel and D. Seebach, Synthesis, 1977, 357 (esp. pp. 380-384).

4. C. A. Brown and A. Yamaichi, Chem. Commun., 1979, 100.

5. L. Wartski, M. El Bouz, J. Seyden-Penne, W. Dumont, and A. Krief, Tetrahedron Lett., 1979, 1543; J. Luchetti, W. Dumont, and A. Krief, Tetrahedron Lett., 1979, 2695.

6. J. A. Thomas and C. H. Heathcock, Tetrahedron Lett., 1980, 3235.

7. Preparative conditions for the anions followed those reported in the literature:

   I: S. Ncube, A. Pelter, K. Smith, B. Blatcher, S. Warren, Tetrahedron Lett., 1978, 2345.
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   IIb: D. Seebach, E. J. Corey, and A. K. Beck, Chem. Ber., 1974, 107, 367.
   IIc: R. D. Balanson, V. M. Kobal, and R. R. Schumaker, J. Org. Chem., 1977, 42, 393.
   III: K. Mori, H. Hashimoto, Y. Takenaka, and T. Takigawa, Synthesis, 1975, 720.

8. Workup: Reaction mixtures were hydrolyzed by addition of methanol and then saturated NH_4Cl. The organic layers were diluted with 1:1 ether-hexane (ether-ethyl acetate with III). HMPTA was removed by extraction six times with 15% aqueous NaCl (each portion = 1ml/mmol HMPTA). After drying with anhydrous Na_2CO_3, the mixture was evaporated and evaporatively distilled (110-115°/3μHg).

9. Analyses of the product ratios was accomplished using highly deactivated glc columns packed with 3% OV101 or Carbowax 20M on Gas Chrom Q.

Received, 8th October, 1981