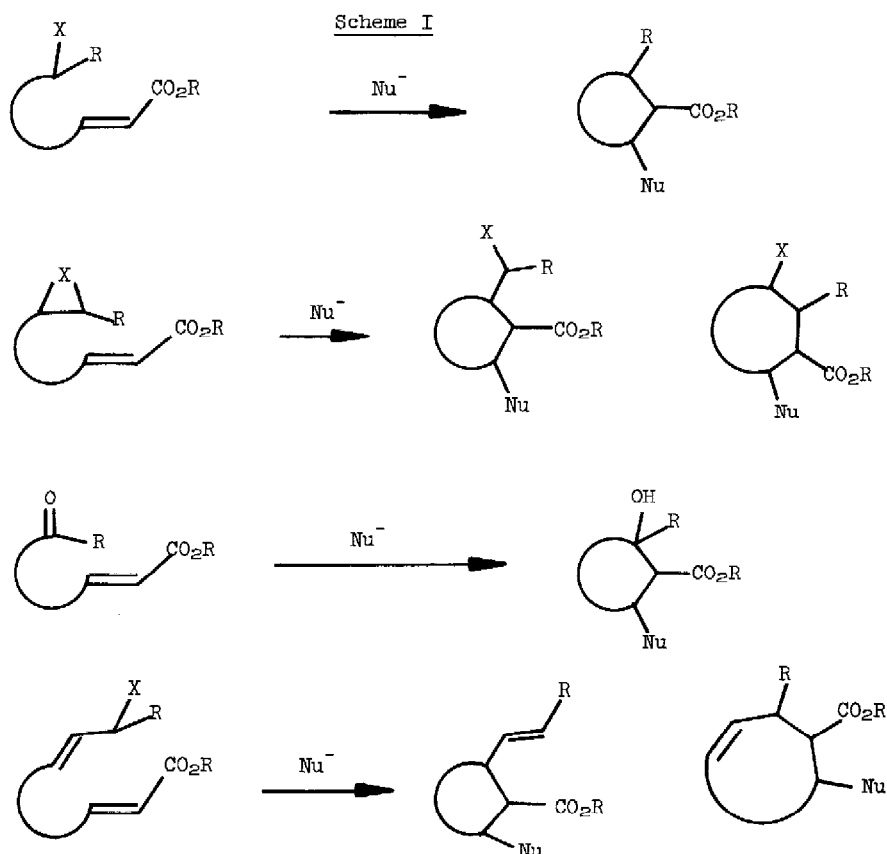


MIRC (Michael Initiated Ring Closure) Reactions
Formation of Three, Five, Six and Seven Membered Rings

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Summary: The term MIRC reaction is defined. Examples of the construction of three, five, six and seven membered rings using alkylthiolates and LDA as nucleophiles are presented.

We define the term MIRC (Michael Initiated Ring Closure) reaction to be applicable to a general set of transformations which are initiated by a conjugate addition to an α,β -unsaturated ester or ketone to produce an enolate which subsequently undergoes intramolecular ring closure. Four possible variations of MIRC reactions are illustrated in Scheme I.



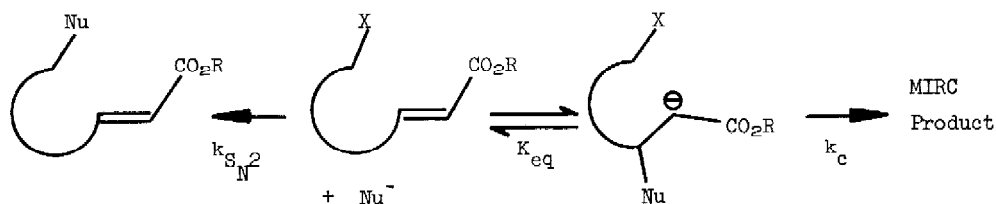
The idea of using a conjugate addition to initiate ring formation has been around for some time. However, many of the examples are limited to cases wherein a carbon (eg., cuprate), rather than a heteroatom centered nucleophile initiates the process, and often to cases wherein the

attacking nucleophilic center is stabilized by a heteroatom which later serves as the leaving group in the ring closure step.¹ More often than not, the methodology has been used to construct cyclopropyl rather than cyclopentyl, cyclohexyl, or cycloheptyl ring systems.² Recently, however, Cooke has reported the formation of five and six membered rings through the addition of several carbon centered nucleophiles to esters of the type $X(\text{CH}_2)_n\text{CH}=\text{CHCO}(\text{PPh}_3)\text{CO}_2\text{Et}$.³ Previously, we reported that sulfur substituted cyclopropyl esters can be synthesized in good yield through the utilization of a MIRC reaction between methyl 4-bromobutenoate and lithium alkylthiolates.⁴ The course of the reaction (MIRC vs $\text{S}_{\text{N}}2$) was shown to be critically dependent upon the choice of solvent and counterion. We were intrigued by these results and, in the interest of extending the scope of MIRC reactions, we initiated the study described below.

We report herein: (a) the use of MIRC reactions to form β -heteroatom substituted cycloalkyl esters of ring size equal to three, five, six, and seven; (b) the use of sulfur and nitrogen (rather than carbon) centered nucleophiles to initiate the MIRC reaction; and (c) the dependence of the reaction path (MIRC vs $\text{S}_{\text{N}}2$) upon the choice of nucleophile.

Table I summarizes the results of our efforts to date. Notice first, that while lithium alkylthiolates can be used to construct three membered rings, attempted closure to a five or a six membered ring leads predominantly to $\text{S}_{\text{N}}2$ and bisaddition ($\text{S}_{\text{N}}2$ plus Michael) rather than a MIRC reaction. On the other hand, the use of lithium diisopropylamide (LDA) as a nucleophile does, in fact, afford five and six membered rings in satisfactory yields (not optimized).^{5,6} Not unexpectedly, attempted closure to a four membered ring is thwarted by side reactions.⁷ Notice also that while the seven membered ring system can be constructed using a MIRC reaction, the yield drops sharply, undoubtedly for entropic reasons. Finally, attempts to close to a five membered ring using alkylthiolate and chloride rather than bromide as the leaving group, leads to both Michael addition and vinylcyclopropane formation rather than an $\text{S}_{\text{N}}2$ or a MIRC reaction.

The results described above can be rationalized using the scheme illustrated below. The rate of formation and the amount of MIRC reaction product formed is clearly dependent upon the



concentration of the enolate as well as the rate constant for closure, k_{c} . The concentration of the enolate is dependent upon K_{eq} which, in turn is related to, among other things, the difference in $\text{p}K_{\text{a}}$ values between the conjugate acid of the nucleophile and the enolate. Therefore, $K_{\text{eq}} < 1$ when the nucleophile corresponds to an alkylthiolate, thereby suggesting that a MIRC reaction should occur only when the rate constant for ring closure, k_{c} , is sufficiently large to make up for the low enolate concentration. Since the rate of ring closure to produce a three membered ring is faster than for closure to a five or a six membered ring,⁸ it is not too surprising that an $\text{S}_{\text{N}}2$ displacement beats out the potentially competitive MIRC reaction in attempts to close to a five or a six membered ring. In fact, even when considering closure to a cyclopropane, the

TABLE I

$\xrightarrow[\text{THF}]{t\text{-BuSLi}}$
 $\xrightarrow[\text{THF}]{\text{ESTER}}$
 $\xrightarrow[\text{THF}]{\text{LDA}}$
 $\xrightarrow{\text{PRODUCT (s) (\%)}}$

PRODUCT (s) (%)	ESTER	THF	PRODUCT (s) (%)
c, h, j a, h, j i, j			d (E)-BrCH=CHCH2CO2CH3 (trace amounts)
b, f, k	(E)-t-BuS(CH2)2CH=CHCO2CH3 (44) t-BuS(CH2)2CH(t-BuS)CH2CO2CH3 (10) (6.3)		a, e (73)
b, f, k	t-BuS(CH2)4CH(SBu-t)CH2CO2CH3 (24) (E)-t-BuS(CH2)4CH=CHCO2CH3 (65)		b, d (53)
—	—		c, d b, l (33) (25)
g, j h, k	Cl(CH2)3CH(t-BuS)CH2CO2CH3 (100) (50)		b, d (30) (44)

a, Yield after distillation; b, Yield after chromatographic purification; vpc yield; d, The nucleophile was added to the ester at -78°C ; e, The ester was added to the nucleophile at -78°C ; f, Thiolate is added until the starting ester disappears (vpc analysis); g, Run in the presence of 3-4 equiv of \underline{t} -BuSH; h, 1.0 equiv of \underline{t} -BuSLi; i, Using KSBu- \underline{t} or NaSBu- \underline{t} ; j, 0°C ; k, room temperature; l, refluxing THF

MIRC and S_N2 reactions are competitive. On the other hand, $1 \ll K_{eq}$ when LDA is used to initiate the MIRC reaction, thereby allowing even the slower five and six membered ring formation to occur in preference to the S_N2 process.

We are continuing to explore other aspects of MIRC reactions including their use in the preparation of bicyclic systems, the use of a wide variety of different nucleophiles so that the chemistry associated with the C-Nu bond in the product can be utilized, and the use of doubly, rather than singly activated esters as substrates.

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- While the conjugate addition of LDA to crotonate esters has previously been noted by Schlesinger, few subsequent reports have appeared. We find the reaction to be general. See: Herrman, T. L.; Kieczkowski, G. R.; Schlessinger, R. H. Tetrahedron Lett., 1973, 2433-2436.
- Attempts to effect a MIRC reaction between methyl 4-bromobutanoate and LDA (-78°C in THF) leads to the formation of significant amounts of polymer-like material; no MIRC product is produced. Presumably, the enhanced acidity of the C-4 hydrogens results in LDA behaving as a base, rather than a nucleophile.
- Cyclobutane ring formation was precluded due to side reactions involving C-4 hydrogen abstraction, subsequent elimination, and, presumably, polymerization; methyl γ -(diisopropylamino)-4-pentenoate was isolated in 48% yield as the only volatile product from the reaction with LDA at -78°C . Cyclopentane formation was immediate at -78°C , and while cyclohexane formation required several hours at this temperature, ring closure was immediate upon warming to room temperature. For best results, formation of the seven membered ring required stirring overnight at room temperature; refluxing in THF produced the same product in less than 15 minutes, albeit in reduced yield.
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