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SEQUENTIAL MICHAEL-MICHAEL-MICHAEL-RING CLOSURE REACTIONS FOR HIGH-YIELD, ONE-POT, 4-COMPONENT COUPLING

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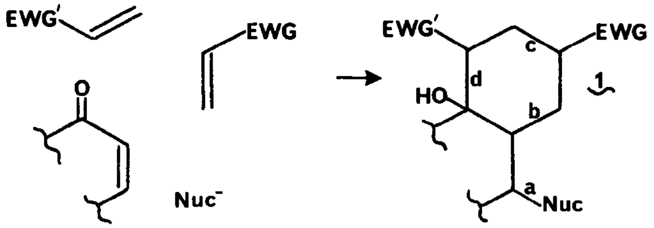
Summary: An extraordinarily easy method is presented for connecting four components leading efficiently to functionalized cyclohexenes, cyclohexanols, cyclodecenones, and aromatic systems.

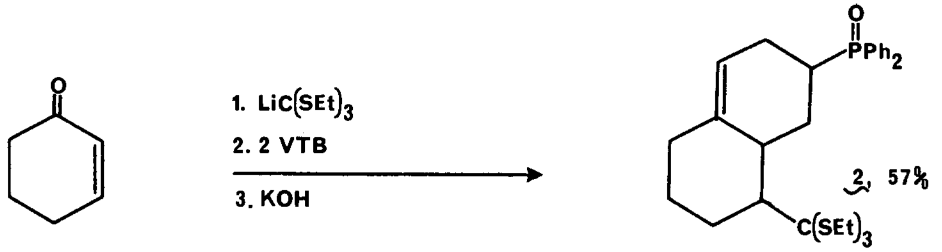
We have developed one-pot, sequential, Michael-Michael-Ring Closure (MIMIRC) reactions for effective construction of various polyfunctionalized cyclohexyl units by coupling of three 2-carbon components.[1-3] Controlled coupling of four components in one reaction vessel is clearly an even more demanding and potentially more useful achievement.[4] We now report successful attainment of this goal as illustrated generally in eq. 1 involving formation of the four bonds a-d in structure 1 and leading to a variety of richly functionalized carbocycles in excellent yields.



(1)

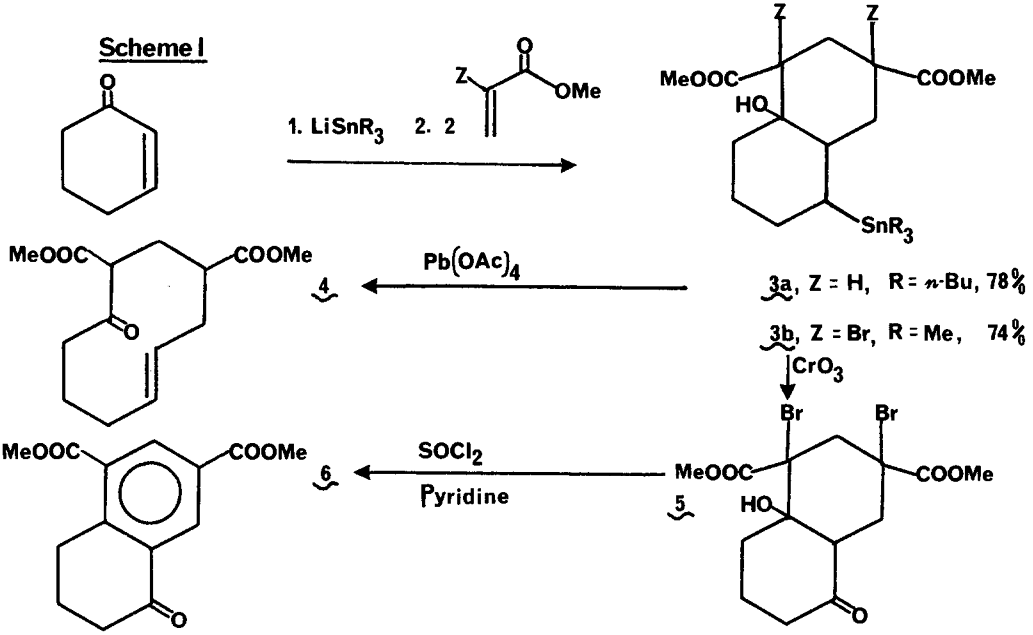
Tris(ethylthio)methyllithium[5] added in a Michael fashion to 2-cyclohexenone to generate an intermediate enolate ion which reacted with two equivalents of vinyltriphenylphosphonium bromide (VTB) under dilute (motor-driven syringe) conditions to give cyclohexannulation product 2 after treatment with potassium hydroxide (to convert the initially-formed phosphonium salt into a more easily isolated phosphine oxide).[1,6] This 4-component coupling reaction (eq. 2) proceeded with an average yield of 83% per each of the four new carbon-carbon bonds!

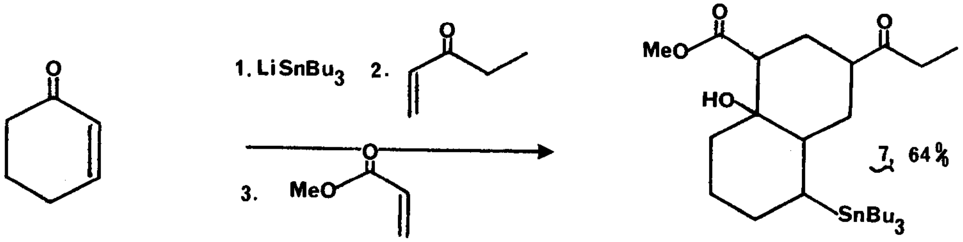
Trialkyltinlithium reagents[7] added in a Michael fashion to 2-cyclohexenone, and the resultant enolate intermediate underwent double Michael addition to two equivalents of methyl acrylate[8] or methyl α-bromoacrylate leading to ester enolate intermediates which spontaneously


1. LiC(SEt)3
2. 2 VTB
3. KOH
PPh2
O
C(SEt)3
2, 57%

(2)

Scheme I


1. LiSnR3 2. 2
Z
OMe
O
MeOOC
COOMe
HO
SnR3
3a, Z = H, R = n-Bu, 78%
3b, Z = Br, R = Me, 74%
CrO3
Pb(OAc)4
4
Br
5
SOCl2
Pyridine
6


1. LiSnBu3 2.
3. MeO
MeO
HO
SnBu3
7, 64%

(3)

underwent intramolecular aldol cyclizations to form polysubstituted cyclohexanols 3a and 3b, each as a mixture of only two diastereomers[2,6] (Scheme I). A motor-driven syringe was not required. This 4-component cyclohexannulation reaction proceeded with a stunning average yield of 93-94% per each new C-C bond! The very rich functionality of annulation products 3a and 3b allows many different further chemical manipulations. For example, the major diastereomer of γ-hydroxystannane 3a was oxidatively cleaved by lead tetraacetate[9] to form highly functionalized *trans*-cyclodecenone 4 in 60% yield;[6] the minor diastereomer of γ-hydroxystannane 3a was likewise oxidatively cleaved to produce the corresponding *cis*-cyclodecenone in 56% yield.[6] This efficient, 2-step conversion of cyclohexenone into a stereodefined, polyfunctionalized cyclodecene system may find use in rapid synthetic entry into the germacrane class of sesquiterpenes.[10] Oxidation of dibromo-γ-hydroxystannane 3b with chromium trioxide[7] afforded dibromo-β-hydroxyketone 5 (50% yield) which was dehydrated and doubly dehydrobrominated (thionyl chloride/pyridine, 0°C → reflux, 1 hour) to form aromatic ketone 6 (64% yield);[6] this overall sequence represents a short, easy and direct means of transforming cyclohexenone into a regiospecifically tetrasubstituted aromatic system having a 1,3,5-tricarbonyl substitution pattern.[11] In this process, the cycloxenone carbonyl group has effectively undergone a 1,3-carbonyl transposition,[12] and the original cyclohexenone -COCH- unit has undergone overall annulation of a *m*-dicarboxylated aromatic ring.

All of the 4-component cyclohexannulations in eq. 2 and in Scheme I involve three different components. An even greater challenge is to couple four different components in a controlled manner. 2-Cyclohexenone reacted sequentially with tri-*n*-butyltinlithium, ethyl vinyl ketone, and methyl acrylate to produce cyclohexannulation product 7 (eq. 3)[6] with an average yield of 86% per new bond! This result is a truly dramatic demonstration of the great synthetical potential of this multi-component coupling process.

Although the sequential Michael-Michael-Michael-Ring Closure (MIMI-MIRC)[1,13] reactions shown here are illustrated only with 2-cyclohexenone as the initial Michael acceptor, our experience already indicates that other α-enones will be usable as well. We are actively pursuing further applications.

ACKNOWLEDGMENT

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3. See the preceding Letter: Posner, G. H., Lu, S.-B. and Asirvatham, E., *Tetrahedron Lett.*, **1986**, *27*, 000.

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