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SEQUENTIAL MICHAEL-MICHAEL-RING CLOSURE REACTIONS FOR 3-DIFFERENT-COMPONENT, ONE-POT, 2+2+2 CONSTRUCTION OF ACYLCYCLOHEXENES AND AN ACYLCYCLOHEXANOL.

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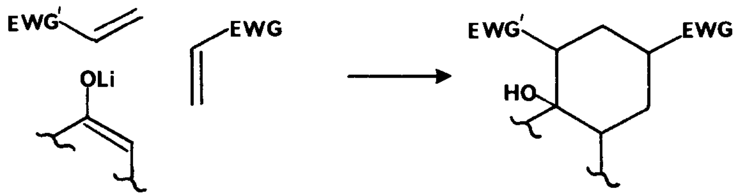
Summary: Two different ketones and a vinylphosphonium salt, separately two different ketones and an acrylate-type ester, and separately a ketone, an unsaturated lactone and a vinylphosphonium salt are linked together in one pot to form new 6-membered carbocycles with average yields of 60-83% per each of three new carbon-carbon bonds (eqs. 2-6).

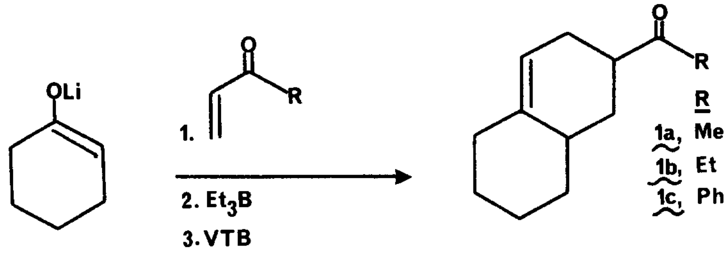
Controlled formation of several carbon-carbon bonds in one reaction vessel is an efficient and rapid way of converting simpler molecules into structurally more complex molecules. We have recently reported such a procedure involving sequential Michael-Michael-Ring Closure (MIMIRC) reactions for one-pot, 2+2+2 construction of phosphorus-substituted cyclohexenes[1] and of alkoxycarbonyl-substituted cyclohexanols.[2] In both cases, as represented in eq. 1, a ketone lithium enolate added to two equivalents of the same Michael acceptor, CH_2=CHEWG, in which the electron-withdrawing group (EWG) was either $-\overset{+}{P}Ph_3$ or -COOR and in which the culminating ring closure step was either a Wittig olefination or an aldol condensation. We have now succeeded in applying this type of MIMIRC sequence to the coupling of three different components: two different ketones and a vinylphosphonium bromide, separately two different ketones and an acrylate-type ester, and separately a ketone, a 2-arylthio-4-butenolide and a vinylphosphonium salt (eq. 1).



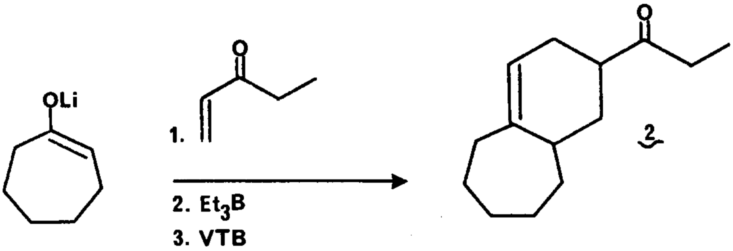
EWG	EWG'
$\overset{+}{P}Ph_3$	$\overset{+}{P}Ph_3$
COOR	COOR
COR	$\overset{+}{P}Ph_3$
COR	COOR
COOR ArS	$\overset{+}{P}Ph_3$

(1)

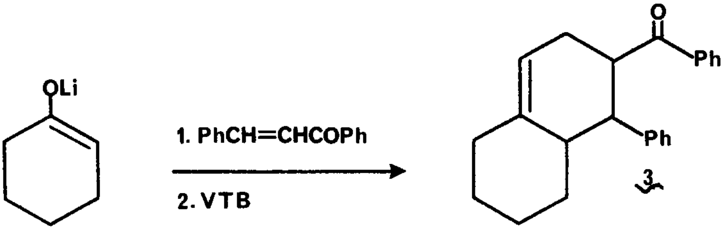
Conventional wisdom indicates that Michael addition of a ketone lithium enolate to a vinyl ketone under aprotic conditions leads to a polymer.[3] To circumvent this problem, Stork and Ganem introduced α-silylenones as tamed Michael acceptors which could be used effectively



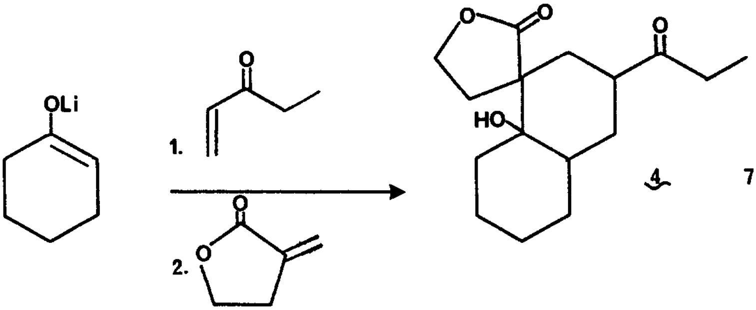
R	% YIELD OF ISOLATED PER BOND	PRODUCT OVERALL	
1a, Me	60	21	(2)
1b, Et	83	57	
1c, Ph	76	44	



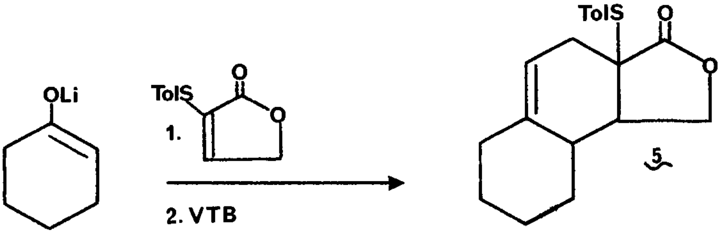
2	71	35	(3)



3	71	35	(4)



4	72	37	(5)



5	64	26	(6)

in Robinson annulations involving single Michael additions.[4] Recently, however, Ziegler and Hwang showed that some reactive vinyl ketones undergo single Michael additions by ketone lithium enolates in aprotic media often without serious undersirable polymerization.[5] We found that cyclohexanone lithium enolate in tetrahydrofuran (THF) at -78°C underwent a single Michael addition to methyl, ethyl, and phenyl vinyl ketones[6] to give a new enolate ion which, in the presence of triethylboron,[1] added to vinyltriphenylphosphonium bromide (VTB) to give, after intramolecular Wittig cyclization, acylcyclohexene annulation products 1a-1c with average yields of 60-83% per new carbon-carbon bond (eq. 2).[7,8] Only in the case of methyl vinyl ketone was polymer observed in significant quantity; somewhat better results were obtained using methyl α-trimethylsilylvinyl ketone (70% average yield per each new carbon-carbon bond). In a similar 2+2+2 MIMIRC sequence, cycloheptanone lithium enolate reacted with one equivalent of ethyl vinyl ketone, with triethylboron, and then with VTB to give acylcyclohexene annulation product 2 with an average yield of 71% per new carbon-carbon bond (eq. 3).[8] Even a β-substituted vinyl ketone could be used successfully as the first Michael acceptor in this sequence: cyclohexanone, chalcone, and VTB gave regiospecifically tetrasubstituted cyclohexene 3 with an average yield of 71% per new carbon-carbon bond (eq. 4).[8]

This one-pot multiple carbon-carbon bond-forming process can be achieved also by combining one equivalent each of two different ketones and an acrylate-type ester. Cyclohexanone lithium enolate added to ethyl vinyl ketone in THF at -78°C and the resultant acyclic enolate intermediate added to α-methylene γ-butyrolactone to produce acylcyclohexanol annulation product 4 with an average yield of 72% per new C-C bond (eq. 5).[8] Adduct 4 represents the kind of synthetically useful, richly-functionalized, tetra-oxygenated molecule which can be assembled efficiently, rapidly, and conveniently by this three-different-component coupling process. Each of the three functional groups in adduct 4 (ketone, lactone, and hydroxyl group) can be manipulated chemospecifically, and formation of the third C-C bond in adduct 4 *via* an aldol condensation represents construction of a hindered spiro-fused β-hydroxycarbonyl system.[2]

The preliminary results reported here indicate that 2+2+2 MIMIRC sequences can be interrupted after only one Michael addition occurs when vinyl ketones are used as the initial Michael acceptors. Finally, equation 6 represents one example in which a 2+2+2 MIMIRC sequence was interrupted after initial Michael addition to 2-toluenethio-4-butenolide; completion of the MIMIRC process with VTB led to acylcyclohexene 5 with an average yield of 64% per new carbon-carbon bond.[8] Further examples of this 3-different-component, 2+2+2, MIMIRC coupling process will add to the already clear, high synthetic potential of this procedure.[9,10]

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7. A typical procedure is as follows: To a dry 100 ml flask fitted with a magnetic stirring bar, an argon inlet, and a serum cap and charged with 1-trimethylsiloxycyclohexene (272 mg, 1.6 mmol) in 2.5 ml of dry THF was added MeLi in Et_2O (1.1 ml, 1.55 *M*, 1.7 mmol) over 2 minutes at 0°C. The reaction mixture was warmed to 25°C with stirring. After 1 hour, the reaction mixture was cooled to -78°C followed by the addition of ethyl vinyl ketone (0.18 ml, 1.8 mmol) over 1 minute. Stirring was continued for 3 hours at -78°C followed by the addition of Et_3B in THF (1.6 ml. 1 *M* , 1.6 mmol) over 1 minute. Stirring was continued for another 1.5 hour at -78°C. Dilution was achieved by the addition of 57 ml of dry THF. VTB (0.915 g, 97%, 2.4 mmol) in 4 ml of dry DMF was added *via* syringe pump over 22 hours while maintaining the reaction mixture at -46°C. Stirring was continued at this temperature overnight. Quenching was achieved by adding saturated NaH_2PO_4 and 5 ml of Et_2O. The organic phase was separated and the aqueous phase was extracted with 2 x 100 ml Et_2O. The combined organic solution was dried (anhydrous $MgSO_4$), filtered, and concentrated. After preparative TLC (40% Et_2O/hexanes) 176.2 mg (57%) of desired product 1b was obtained: NMR ($CDCl_3$, 80 MHZ) δ: 1.04 (3H, t, J=7.3 Hz), 2.49 (2H, g, J=7.3 Hz), 1.0-2.4 (14H) 5.29 (1H, m); IR (CCl_4, cm^{-1}): 1700; High resolution mass spectrum (M^+): Calcd., 192.1514, Found: 192.1509.
8. Yields are reported for pure products isolated by preparative TLC; all new compounds were fully characterized spectroscopically and by combustion microanalysis and/or high resolution mass spectra.
9. See the following Letter: Posner, G. H. and Asirvatham, E., *Tetrahedron Lett.*, **1986**, 27, 000.
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