Intramolecular Dimerization of Carbenoids

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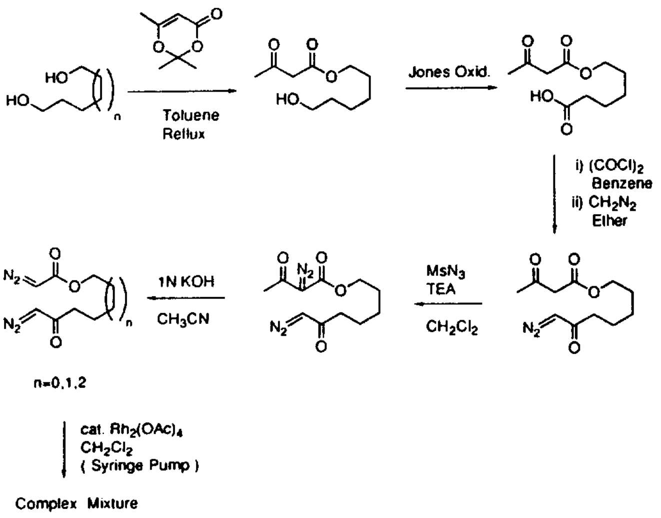
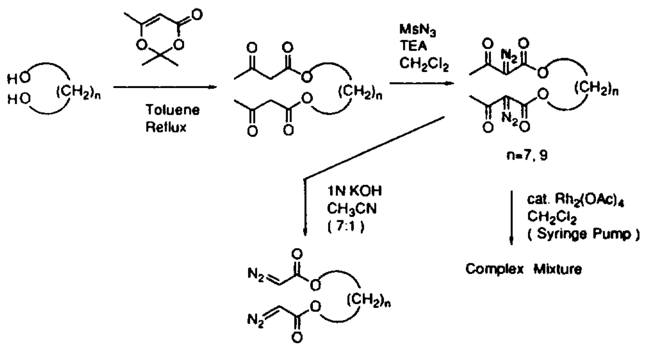
Inter- and intramolecular cyclopropanation and intramolecular C-H bond insertion of α-diazocarbonyl compounds are now well-established and important C-C bond forming reactions in organic synthesis, involving metal-carbene complexes.[1,2] Less well developed is the formation of C-C double bonds *via* metal catalized dimerization of α-diazocarbonyl compounds. Only a few examples of intramolecular dimerization of bis-α-diazoketones are known. Bullvalene[3] and γ-tropolone[4] were synthesized *via* Cu-catalized dimerization of bis-α-diazoketones albeit in low yield. More recent reports on reasonably facile (although unintended) intermolecular dimerization reactions of diazoacetates[5] and α-diazoketones[6] prompted us to study the efficiency in the intramolecular version of these reactions.

Diazoacetoxy-α-diazoketones were initially chosen as possible candidates for intramolecular dimerization as they should lead to the formation of unsaturated ketolactones as encountered in patulolide-type natural products.[7] They were synthesized from diols *via* acetoacetylation, Jones oxidation, conversion of the acids to acid chlorides followed by diazomethane treatment, and subsequent diazo transfer[8] and deacetylation (Scheme 1). Unfortunately, treatment of these diazoacetoxy-α-diazoketones ($n=0$, 1, 2) with catalytic amount of rhodium acetate under high dilution conditions resulted in the formation of intractable mixture of products.

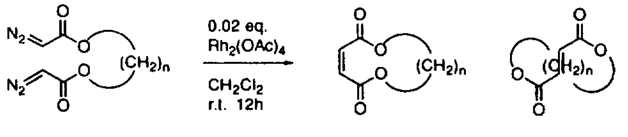
Next, bis-α-diazoacetoacetoxyalkanes and bis-diazoacetoxyalkanes were synthesized from diols *via* corresponding bis-acetoacetates (Scheme 2). Bis-α-diazoacetoacetoxyalkanes ($n=7$, 9) reacted with catalytic amount of rhodium acetate to yield very complex product mixtures.



Scheme 1.



Scheme 2.



	Isolated Yield (%)		
n=2	57 (Mixture of Dimers)		
n=3	67 (cis only)		
n=4	46 (cis only)		
n=5	54 (cis only)		
n=6	42	4 : 1	
n=7	52	3 : 1	
n=8	57	1.5 : 1	
n=9	59	2 : 1	

Scheme 3.

Bis-diazoacetoxyalkanes, on the other hand, were converted to cyclic products in useful yield under standard conditions. Reaction of bis-diazoacetoxypropane, -butane, and -pentane yielded only cyclic maleate esters, and bis-diazoacetoxyhexane, -heptane, -octane, and -nonane yielded both maleate and fumarate cyclic esters[9] (Scheme 3). Bis-diazoacetoxyethane was converted into a mixture of dimeric ring products in lower yield.

In conclusion, intramolecular dimerization of certain class of bis-α-diazocarbonyl compounds can be used in the synthesis of large ring products and bis-diazoacetoxyalkanes may serve as viable precursors of cyclic maleates and fumarates.

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Construction of Contiguous Quaternary Carbon Centers by Intramolecular Addition of Tertiary Radicals to Activated Olefins

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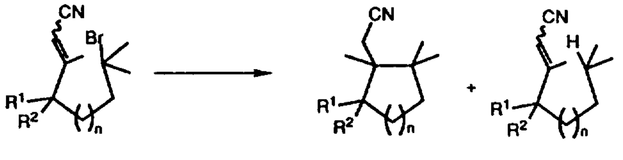
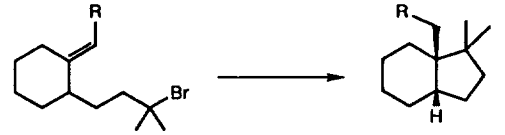
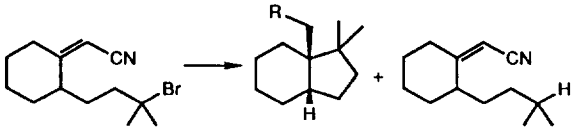
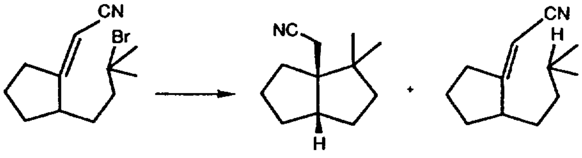
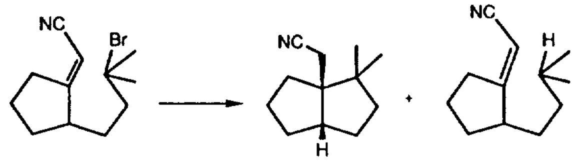
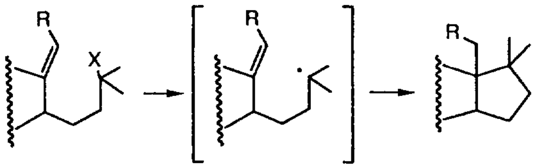
Even though various synthetic methodologies have been developed, construction of quaternary carbon centers still remains a challenging task to synthetic chemists.[1,2] Addition of free radicals to alkenes has enjoyed increasing popularity for the formation of carbon-carbon bonds due to its advantages over the ionic reactions. Free radical addition to alkenes, however, has been noted for its sensitivity to steric environment. For example, the radical cyclization rates are decreased as steric hindrance at the site of attack is increased. Free radical addition to alkenes for the construction of sterically congested environment have hardly been systematically investigated.[2d,3] Here we report a successful free radical addition in intramolecular mode for the formation of *contiguous* quaternary carbon centers. We envisioned that smaller SOMO-LUMO energy gap employing tertiary alkyl radicals and olefins having electron withdrawing groups which has lower LUMO energy might overcome the constraints created by steric congestion. This will add another option for the construction of contiguous quaternary carbon centers in addition to the method *via* the Michael reaction[2a] and *via* the addition on benzyllithium to carbon-carbon double bonds.[2c]

We have investigated the intramolecular cyclization *via* the radical intermediates directly generated from the corresponding tertiary bromides[4] to construct the contiguous quaternary carbon centers represented by the Eq. (1).

Table 1. Radical Cyclization to Construct Contiguous Quaternary Carbon Centers[6]

Entry	Bromide	Stereochemistry of olefin	Product(Yield)	
				
1	n=1, $R^1=H$, $R^2=H$,	(*E*)	(75%)	–
2	n=2, $R^1=H$, $R^2=H$,	(*E*)	(64%)	(15%)
3	n=1, $R^1=CH_3$, $R^2=H$,	(*Z*)	(62%)	(13%)
4	〃	(*E*)	(32%)	(22%)
5	n=1, $R^1=CH_3$, $R^2=CH_3$,	(*E*)	(73%)	–
				
6	R=CN	(*E*)	1 (88%)	
7	R=Ph	(*E*)	(45%)	
				
8		(*Z*)	(50%)	(30%)
				
9		(*Z*)2	(63%)	(7%)
				
10		(*E*)	(43%)	(20%)

 (1)

The results of the cyclizations are summarized in Table 1. All the substrates for radical cyclization were prepared by the Witting reaction of the corresponding ketones. (*E*)- and (*Z*)-isomers separated by HPLC.[5] Cyclizations[6] usually proceeded in good yields despite the disadvantages in steric environment. All the cyclization proceeded in 5- or 6-*exo*-trigonal modes and we were unable to detect the products from 6-*endo*- or 7-*endo*-trigonal cyclization. Activation of the terminal site of the double bond is required and nitrile group