Synthesis of Cyclopent-2-enones through Stepwise [3 + 2] Cycloaddition of Simple Silyl Enol Ethers and Alk-1-ynes

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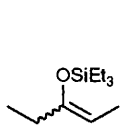
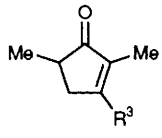
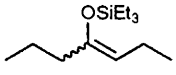
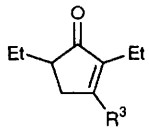
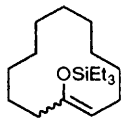
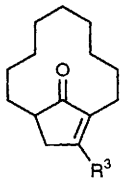
Treatment of silyl enol ethers and alk-1-ynes with $SnCl_4$–Bu_3N reagent followed by DBU, leads to cyclopent-2-enones, through [3 + 2] cycloaddition reactions; the initial carbon–carbon bond formation is carbometallation of alkynes, and the second step is a base-promoted intramolecular alkylation which reductively eliminates tin species (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene).

[3 + 2] Cycloaddition of enolate derivatives with carbon–carbon multiple bonds is an attractive method to construct cyclopentanone nuclei. During our investigations on activation of alk-1-ynes with $SnCl_4$–Bu_3N reagent,[1] we found a novel stepwise [3 + 2] cycloaddition of silyl enol ethers **1** and alk-1-ynes **2**. This cyclopent-2-enone synthesis involves carbometallation of alkynes and subsequent intramolecular alkylation which reductively eliminates the tin species. When compared with related cycloaddition reactions using oxyallyl cations,[2–4] the following synthetic aspects are characteristic; (*i*) This reaction employs simple silyl enol ethers instead of α-haloenolates for the three-carbon unit. (*ii*) Aliphatic and aromatic alk-1-ynes are used for the two-carbon unit, while the conventional reactions were conducted with olefins possessing cation-stabilizing groups, *e.g* styrenes, enamines, or dienes.

Silyl enol ethers **1** and alk-1-ynes **2** were treated with $SnCl_4$ and Bu_3N in refluxing MeCN for 1 h; DBU was then added, and refluxing continued for 30 min. As shown in Table 1, cyclopent-2-enones **4** were obtained in good yields from the reaction of several alk-1-ynes and silyl enol ethers derived from methylene ketones.† A simple synthesis of bicyclo[9,2,1]tetradecenone derivatives is notable. Using Me_3CN as the solvent and the stepwise addition of the reagents gave good results. Higher yields are attained with triethylsilyl or *tert*-butyldimethylsilyl enol ethers compared with trimethylsilyl derivatives, which formed a substantial amount of enones **5** and other byproducts.

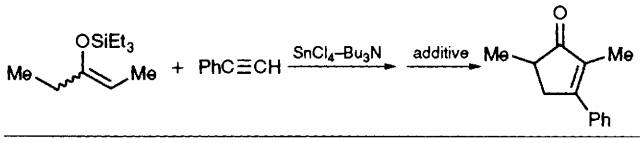
Previous studies have revealed that (*Z*)-allyltin **3** is formed from **1** and **2** in the presence of $SnCl_4$ and Bu_3N.[1] Accordingly, **4** must be the cyclization product of **3**, and the overall process can be envisaged as a stepwise [3 + 2] cycloaddition. The added amine is essential for the second carbon–carbon bond formation; the effects of other amine additives studied are shown in Table 2. Hindered and non-nucleophilic amines such as DBU, 1,8-bis(dimethylamino)naphthalene, Bu_3N, or 2,6-di(*tert*-butyl)-4-methylpyridine are effective. It appears that basicity is not an important factor. Using chiral amines, (−)-brucine or (*R*)-*N*-(1-phenylethyl)pyrrolidine, lead to racemic cyclopentenones. Inorganic salts such as LiCl or KF also show some activity. It may be reasonable to assume that

Table 1 [3 + 2] Cycloaddition reaction of silyl enol ethers and alk-1-ynes

Silyl enol ether[a]	R^3	Product[b]	Yield (%)[c]
			
	n-C_5H_{11}		53
	$PhCH_2CH_2$		54
	Ph		70
	p-ClC_6H_4		64
	p-$MeOC_6H_4$		62
			
	n-C_5H_{11}		54
	Ph		74
			
	n-C_5H_{11}		39
	Ph		61

[a] Mixtures of (*E*)- and (*Z*)-isomers were used. [b] All the products gave satisfactory ^1H NMR, ^{13}C NMR, IR and MS spectra and elemental analysis either by combustion or high resolution MS. [c] Isolated yields are shown.

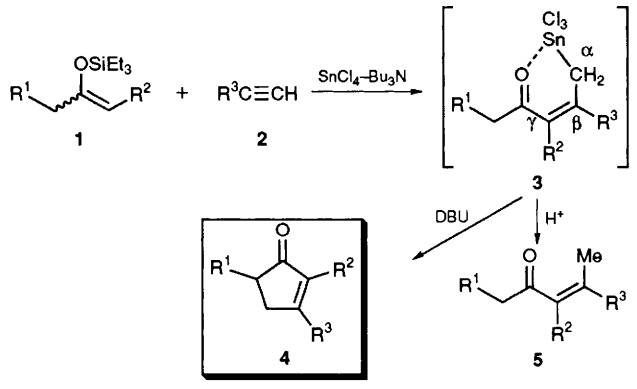
Table 2 Effects of additives



Additive	Yield (%)
None	5
DBU	70
1,8-Bis(dimethylamino)naphthalene	56
Bu_3N	66
Pr^i_2NH	61
(−)-Brucine	39
(*R*)-*N*-(1-Phenylethyl)pyrrolidine	58
N,*N*,*N*′,*N*′-Tetramethylethylenediamine	5
Pyridine	11
2,6-Di(*tert*-butyl)-4-methylpyridine	53 (11)[a]
Bu_3P	12
Hexamethylphosphoramide	20
Me_2SO	14
LiCl	10
KF	26

[a] Yield of a byproduct, 5-acetyl-2,5-dimethyl-3-phenylcyclopent-2-enone, formed by acylation of the product with acetonitrile.

† *Typical procedure*: Under an argon atmosphere, **1** (R^1 = Et, R^2 = Et) (343 mg, 1.5 mmol) in MeCN (1.5 ml) was added to a MeCN (1.5 ml) solution of $SnCl_4$ (0.18 ml, 1.5 mmol) at room temp. After stirring for 15 min at room temp. **2** (R^3 = Ph) (102 mg, 1.0 mmol) in Me_3CN (1 ml) and Bu_3N (0.05 ml, 0.2 mmol) were added successively, and the mixture was stirred for 1 h under reflux. DBU (0.19 ml, 1.3 mmol) was then added, and refluxing was continued for 30 min. The mixture was poured on a saturated cooled $NaHCO_3$ (aq) and filtered. Organic materials were extracted with ethyl acetate, washed with $KHSO_4$ (aq) and brine, dried, concentrated, and chromatographed over alumina giving **4** (R^1 = Et, R^2 = Et, R^3 = Ph) (159 mg, 74%).



Scheme 1

these additives promote enolization of **3**, and intramolecular alkylation gives the cyclization products **4**, where $SnCl_3$ functions as a leaving group[5,6] liberating Sn^{II} species.[7] This reductive elimination redeems the use of the simple enolates in the present [3 + 2] cycloaddition instead of α-haloenolates. Takeda *et al.* have reported related reductive alkylation reactions with allyltins under Lewis acidic conditions,[5] whereas here the alkylation is under basic conditions.

The following substituent effects on this cyclization reaction disclose some properties of the reductive leaving group. (*i*) Cyclopentenone was not obtained from silyl enol ether **1** (R^1 = H, R^2 = $PhCH_2$) and **2** (R^3 = Ph). Since **3** (R^1 = H, R^2 = $PhCH_2$, R^3 = Ph) is formed in a high yield by the carbometallation reaction,[1] the unfavourable result is attributable to inefficiency at the cyclization process. The unsusceptibility of the methyl ketone to cyclization compared with methylene ketones is pertinent to the reactivity of the corresponding enolates.[8] (*ii*) The reaction proceeds with aliphatic alkynes as well as aromatic alkynes, and β-substituents R^3 of **3** do not have much effect on the cyclization. (*iii*) Allyltin **3** (R^1 = $PhCH_2$, R^2 = H, R^3 = Ph or *n*-C_5H_{11}) generated from silyl enol ether **1** (R^1 = $PhCH_2$, R^2 = H) gives **4** (R^1 = $PhCH_2$, R^2 = H, R^3 = Ph or *n*-C_5H_{11}) in low yields. Serious decomposition of **3** takes place on the base treatment. Removal of the γ-substituent R^2 inhibits the cyclization. The substituent effects (*ii*) and (*iii*) suggest some similarity of this reductive alkylation to nucleophilic substitution reactions of allyl halides.[9,10]

In summary, a stepwise [3 + 2] cycloaddition reaction of simple silyl enol ethers and alk-1-ynes gives cyclopent-2-enones; the $SnCl_3$ group functions as a reductive leaving group in the base-promoted enolate alkylation reaction.

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