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The Use of Silyl Enol Ethers in the Alkylation of Substituted Cyclanones.

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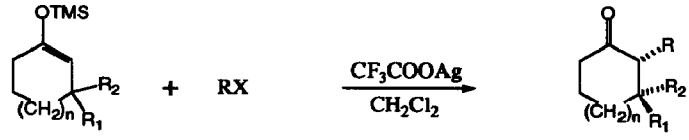
Key Words : Alkylation, alkyl halide, conjugate addition, silver trifluoroacetate, silyl enol ether.

Abstract: *The reactions of 1-(trimethylsiloxy)-3-methylcyclopent-1-ene, 1-(trimethylsiloxy)-3-methylcyclohex-1-ene and 1-(trimethylsiloxy)-3,3-dimethylcyclohex-1-ene with various alkylating agents in the presence of silver trifluoroacetate produced the corresponding 2,3-dialkylated and 2,3,3-trialkylated cyclanones with high regiodifferentiation and stereoselection.*

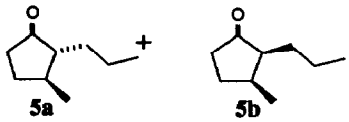
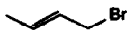
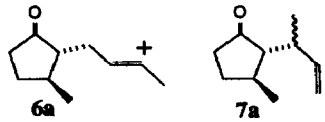
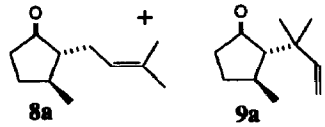
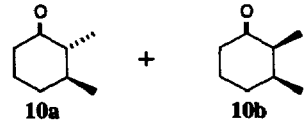
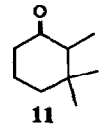
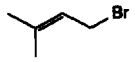
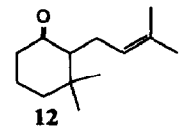
The potential nucleophilicity of carbonyl compounds in a controlled alkylation reaction presents some limitations[1] because of competing reactions (condensation, O-alkylation, polyalkylation, etc.).[2] Thus, the generation of particular lithium enolates has become an important step in order to avoid enolate equilibration, in the case of unsymmetrical substituted ketones. A general method of obtaining enolates specifically consists in effecting a conjugate addition of dialkylcuprates[3] or Grignard reagents[4] to cycloalkenones in the presence of a catalytic amount of copper(I) halide. Subsequent substitutions require a large excess of alkylating agent and are limited to methyl iodide and allyl halides.[5] In an alternative approach, the enolate anion is trapped *in situ* with chlorotrimethylsilane and regenerated using methyllithium[6] or lithium amide in liquid ammonia in which proton transfer is minimized.[7] Generally, when the cleavage of trimethylsilyl enol ethers with methyllithium precedes substitution, alkylation does not occur without the formation of other products.[6] Thus, the use of silyl enol ether with Lewis acids[8] which induce α-alkylation, appeared to be a very attractive approach. The reaction, in presence of $ZnCl_2$, $TiCl_4$ and $SnCl_4$, which consists in the formation of the corresponding carbocation, is limited to S_N1 active halides.

Examination of the literature showed that silver trifluoroacetate can be used efficiently in such processes with non activated primary alkyl halides.[9] Trimethylsilyl enol ethers of 3-methylcyclopentan-1-one (**1**), 3-methylcyclohexan-1-one (**2**) and 3,3-dimethylcyclohexan-1-one (**3**)[6a] were chosen to illustrate this method.



1 - 3 **4 - 12**

Table I. Alkylation of 1-trimethylsiloxy-3-methylcyclopent-1-ene (**1**), 1-trimethylsiloxy-3-methylcyclohex-1-ene (**2**) and 1-trimethylsiloxy-3,3-dimethylcyclohex-1-ene (**3**).[a]

entry	silyl enol ether	alkyl halide[b]	CF_3CO_2Ag (equiv.)	Temp. (°C)	Products	Ratio	Yield (%)[c]
1)	**1**	MeI	1.05	-78→rt	 **4a** + **4b**	6.1 : 1[d]	78
2)	**1**	MeI	1.60	-78→rt	**4a** + **4b**	5.7 : 1[d]	74
3)	**1**	MeI	1.60	0→rt	**4a** + **4b**	4.7 : 1[d]	72
4)	**1**	MeI	1.60	rt	**4a** + **4b**	4.0 : 1[d]	72
5)	**1**	n-PrI	1.05	-78→rt	 **5a** + **5b**	9.8 : 1[d]	54
6)	**1**		1.05	-78→rt	 **6a** + **7a**	3.7 : 1[e,f]	66
7)	**1**		1.05	-78→rt	 **8a** + **9a**	3.8 : 1[e]	61
8)	**2**	MeI	1.05	-78→rt	 **10a** + **10b**	11 : 1[d]	60
9)	**3**	MeI	1.05	-78→rt	 **11**		35
10)	**3**		1.05	-78→rt	 **12**		22

[a]All alkylations were carried out in CH_2Cl_2 (1ml/mmol); [b]halides and silver trifluoroacetate are used in equimolar quantities; [c]yields were determined by quantitative glc analysis using an internal standard; remaining products are unreacted and hydrolyzed silyl enol ethers; [d]*trans* : *cis*-isomers; [e]regioisomers; [f]1:1 mixture of *threo* : *erythro* products.

2,3-Disubstituted cyclopentanones and cyclohexanones constitute important synthons for the preparation of naturally occurring and biologically active compounds.

The alkylation process is an effective route in presence of silver trifluoroacetate, as has been demonstrated previously with unsubstituted cyclic ketones.[9c] Methylation of 1-trimethylsiloxy-3-methylcyclopent-1-ene (**1**), available by conjugate addition of lithium dimethylcuprate to cyclopent-2-en-1-one, is first explored in various reaction conditions and is reported in Table I.

Results of the reaction of 1-(trimethylsiloxy)-3-methylcyclopent-1-ene (**1**) with methyl iodide clearly show that the monomethylated compound **4a** is formed in a regio- and stereoselective manner (entry 1). The use of equimolar quantities of silyl enol ether, methyl iodide and silver trifluoroacetate affords 2,3-dimethylcyclopentanone **4a** and **4b** in high yield. An excess of methyl iodide and silver trifluoroacetate (entry 2) decrease the formation of **4a** and the yield of the reaction. Raising the reaction temperature (entries 3 and 4) also favoured the formation of the *cis*-isomer **4b**. Experiments at -78°C of silyl enol ether **1** with propyl iodide led to the formation of the *trans*-isomer **5a** with high stereoselectivity (entry 5). These results, compared to those previously obtained with alternative methods, underline the utility of silver trifluoroacetate.

The reactions of **1** with crotyl and prenyl bromides (entries 6 and 7) show notable differences from that observed for 2-(trimethylsiloxy)furan with prenyl bromide.[10] For example, while the present method leads to the formation of products **7a** and **9a**, resulting from allylic rearrangment, with the furan derivative, only the product of primary alkylation was found. However, our results are similar to those previously reported for silyl enol ether of cyclopentanone with prenyl bromide and $ZnCl_2$.[11] These apparently conflicting findings can be easily explained by the greater reactivity of 2-trimethylsiloxyfuran. Together, entries 6 and 7 strongly suggest that allylic bromides react by an S_N1 type mechanism. It seems that the structures of the alkylating agent and of the silyl enol ether play a crucial role not only in influencing the yield, but also in determining the reaction mechanism; alkylation competes with Lewis acid induced isomerization.

In a somewhat similar way, treatment of 1-(trimethylsiloxy)-3-methylcyclohex-1-ene (**2**) with methyl iodide, gives the *trans*-isomer stereoselectively (*trans* : *cis* , 11 : 1). This result may be attributed to conformational features of six-membered cycloalkanones which disfavour the formation of the *cis*-isomer. Reaction of 1-(trimethylsiloxy)-3,3-dimethylcyclohex-1-ene (**3**) with methyl iodide affords **11** regio-selectively, with a 30% yield (entry 9) and, with prenyl bromide, produces only the prenylated adduct. The tertiary isomer is not observed because of strong steric effects at the β-carbon. This result is in agreement with those previously reported for sterically demanding substrates.[11]

In conclusion, silver trifluoroacetate catalyzes the alkylation of the silyl enol ethers with primary alkyl halides, producing regio- and stereoselectively and in moderately high yields, 2,3-disubstituted cyclanones, uncontaminated with polyalkylated and polymeric compounds. Allylation with crotyl and prenyl bromides gives products arising from attack at the primary and secondary/tertiary carbons, suggesting S_N1 and S_N1' type mechanisms. A valuable characteristic of the present method resides in the use of an equimolar quantity of alkylating agent, which contrasts with enolate mediated alkylations. Consequently, this reaction, from a synthetical point of view, is extremely interesting.

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