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Studies on the reactions of α,β-enones with allyl indium reagent; effects of TMSCl as promoter on regioselectivity

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Abstract—Regioselectivity on the reactions of α,β-enones with allyl indium reagents in the presence of TMSCl was systematically studied. 2-Cyclohexen-1-one, (*R*)-carvone, 2-cyclohepten-1-one and chalcone produced 1,4-addition products in good yields, whereas 2-cyclopenten-1-one, 2-methylcyclopenten-1-one, 4,4-dimethylcyclohexen-1-one and acyclic α,β-enones afforded 1,2-addition products. © 2000 Elsevier Science Ltd. All rights reserved.

The conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is one of the most useful and reliable methods for carbon–carbon bond formation. It has been normally achieved using organocopper reagents and Grignard reagent in the presence of catalytic copper(I) halide.[1] Our interests, both in extending the scope of the Michael addition reaction and applying indium metal to modern organic synthesis, have led to the investigation of the indium promoted Michael addition reaction. Generally, organoindium reagents reacted with α,β-unsaturated aldehydes to afford 1,2-addition products in good yields.[2] Reaction of 4-phenyl-3-buten-2-one, which is a unique example of a simple α,β-unsaturated ketone, with organoindium reagents produce a regioselective 1,2-addition product.[2a,b] However, there are few reports on Michael addition reaction to simple α,β-unsaturated ketones using allyl indium reagents. Recently, it was reported that indium-mediated addition of allyl bromide to 1,1-dicyano-2-arylethenes gave Michael addition products in aqueous media with good yields.[3] Tetraorganoindium ate complexes reacted with α,β-unsaturated ketones in a 1,4-addition fashion.[4] The reaction of allylic indium sesquihalides with α,β-unsaturated carbonyl compounds, in which two electron withdrawing groups were attached to alkenes, proceeded in a 1,2-addition mode, whereas a 1,4-addition reaction took place with 1,1-dicyano-2-arylethenes, which are extremely electron deficient olefins.[5] Although lots of examples on the indium-mediated allylation to aldehydes and ketones have been reported,[6] as far as we are aware, no systematic studies on the regioselective allylation to simple α,β-unsaturated ketones such as 2-cyclohexen-1-one have been published. As part of our continuing effort to expand the synthetic utility of indium, we now report the results on the reaction of simple α,β-unsaturated ketones with allyl indium reagents and the effects of trimethylsilyl chloride as a promoter on regioselectivity.

Table 1 summarizes the experimental results and illustrates the efficiency and scope of the present method.[7] Initial studies were performed with the reaction of 2-cyclohexen-1-one (entry 3, Table 1), which reacted regioselectively with allyl indium reagent to produce a 1,2-addition product in 60% yield. Although a catalytic amount of copper iodide was added to reaction mixture, 1,2-addition product was obtained only in 60% yield. However, when a catalytic amount of copper iodide in the presence of TMSCl as additive was used, silyl enol ether of 3-allylcyclohexanone was obtained in 44% yield by 1,4-addition of allyl indium reagent followed by enolate trapping. Moreover, 2-cyclohexen-1-one was treated with allyl indium reagent in the presence of 5 equivalents of TMSCl to produce 3-allylcyclohexanone, which is 1,4-addition product, in 63% yield.[8] Surprisingly, 2-cyclopenten-1-one did not react with allyl indium reagent. When 2-cyclopenten-1-one reacted with allyl indium reagent in the presence of TMSCl, a 1,2-addition product was obtained in 54% yield (entry 1, Table 1). On the basis of these results, the reactivity of the allyl indium reagent is lower than allylic cuprates or Grignard reagents. Treatment of

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Keywords: indium; Michael reaction; promoter.

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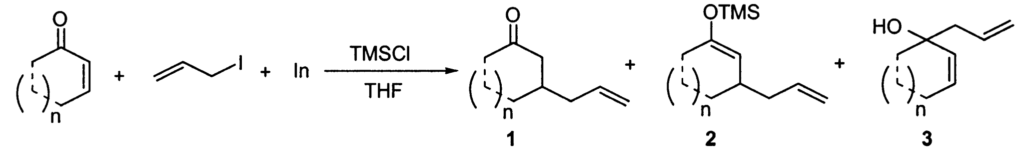
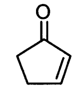
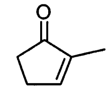
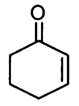
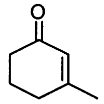
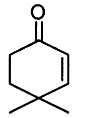
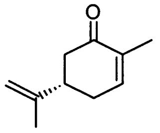
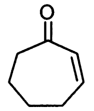
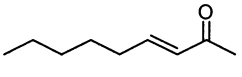
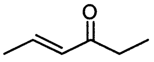
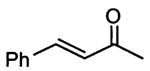
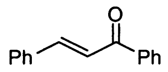
(*R*)-carvone and 2-cyclohepten-1-one with allyl indium reagent using TMSCl gave 1,4-addition products in 70 and 61% yields, respectively (entries 6 and 7, Table 1), whereas 2-methylcyclopenten-1-one and 4,4-dimethyl-2-cyclohexen-1-one produced 1,2-addition products in spite of the presence of TMSCl (entries 2 and 5, Table 1). 3-Methylcyclohexen-1-one did not reacted with allyl indium reagent in the presence of 1 equivalent of

Table 1. Reactions of allyl indium reagents with α,β-enones in the presence of TMSCl



entry	α,β-enone	reaction conditions[a]	time (h)	isolated yield / %		
				1	2	3
1		C	0.5			54
2		C	0.5			62
3		A/0.1eq CuI	1		44	
		A[b]/0.1eq CuI	1			60
		B	0.5	63		
		C[b]	0.5			60
		C	0.5	55		
4		D	24	0[c]		
5		C	0.5			54
6		D	0.5	70(1.4:1)[d]		
7		B	0.5	61		
8		A	0.5			77
		B		0[c]		
		C[b]	0.5			60
		C	0.5			80
9		C	0.5			73
10		C	0.5			61
11		B	0.5			42(25)[e]
		D	0.5	75		

[a] Reaction conditions(In:allyl iodide:TMSCl) : A=1:1.5:1, B=1:1.5:5, C=2:3:1, D=2:3:5. [b] TMSCl was not used. [c] messy. [d] The diastereomeric ratio. [e] The yield of the recovered starting material.

TMSCl. The use of 5 equivalents of TMSCl gave a complex mixture of products (entry 4, Table 1). We next turned our attention to acyclic α,β-unsaturated ketones. Although TMSCl was used as additive, 1,2-addition products were generally obtained in good yields (entries 8, 9 and 10, Table 1). It was noteworthy that yield was increased when TMSCl was used (entry 8, Table 1). However, treatment of chalcone with allyl indium reagent in the presence of 5 equivalents of TMSCl produced the 1,4-addition product in 75% yield.

In summary, regioselectivity on the reactions of α,β-enones with allyl indium reagents in the presence of TMSCl was systematically studied. 2-Cyclohexen-1-one, (*R*)-carvone, 2-cyclohepten-1-one and chalcone produced 1,4-addition products in good yields, whereas 2-cyclopenten-1-one, 2-methylcyclopenten-1-one, 4,4-dimethylcyclohexen-1-one, 3-nonen-2-one, 4-hexen-3-one and 4-phenyl-3-buten-2-one afforded 1,2-addition products. Generally, TMSCl increase the yields of 1,4- or 1,2-addition products. However, excess TMSCl gave a complex mixture of products. Because α,β-enones except 1,1-dicyano-2-arylethenes reacted with ally indium reagents in a 1,2-addition fashion and no studies of the Michael addition reaction to α,β-enones using organoindium reagents have been published, the present method contrasts with and complements the existing synthetic methods. Although the role of TMSCl is not completely understood, it may be explainable in terms of Lewis acid which activates the carbonyl group and the softness of these reagents. Further studies on the relation between the 1,2/1,4-selectivity and the α,β-enone structure are now in progress.

Acknowledgements

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7. All new compounds have satisfactory analytical data including ^{1}H, ^{13}C NMR, MS and IR spectra.
8. To a solution of indium (115 mg, 1.0 mmol) in THF (3 mL) was added allyl iodide (252.0 mg, 1.5 mmol) under nitrogen at room temperature. After stirring for 1 h, 2-cyclohexen-1-one (96.0 mg, 1.0 mmol) and chlorotrimethylsilane (543.0 mg, 5.0 mmol) was added to reaction mixture. After 30 min, the reaction mixture was poured into pH 8.0 buffer solution (10 mL, Na_2HPO_4/NaH_2PO_4), which was pre-cooled at 0°C. The aqueous layer was extracted with ether (3×25 mL) and the combined organic layer washed with water (20 mL), brine (20 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20/1) leading to 3-allylcyclohexanone (87 mg, 63%).