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Synthesis of Water-Tolerant Indium Homoenolate in Aqueous Media and Its Application in the Synthesis of 1,4-Dicarbonyl Compounds via Palladium-Catalyzed Coupling with Acid Chloride

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Abstract: The first water-tolerant, ketone-type indium homoenolate was synthesized via the oxidative addition of In/$InCl_3$ to enones. The reaction proceeds exclusively in aqueous media. Both indium and indium(III) chloride are necessary for the smooth conversion of the reaction. Similar results were obtained when InCl or $InCl_2$ was used in place of In/$InCl_3$. The synthetic utility of the indium homoenolate was demonstrated through the synthesis of 1,4-dicarbonyl compounds via palladium-catalyzed coupling of indium homoenolate with acid chloride.

Homoenolate,[1] a species containing an anionic carbon β to a carbonyl group, is a potentially very useful three-carbon synthon for organic synthesis. Therefore, there has been increasing interest in the preparation and application of metal homoenolates in organic synthesis.[2−4] However, the use of metal homoenolates in organic synthesis has not been fully explored, probably due to the limited methods available for the facile generation of metal homoenolates. Among the several methods developed for the synthesis of metal homoenolate,[2−4] the most commonly used method is pioneered by Kuwajima and Nakamura via ring-opening of siloxycyclopropane with various metal halides.[2] Later, Yoshida and co-workers reported the synthesis of zinc homoenolates via oxidative addition of zinc to β-iodoesters.[3] It is worthwhile to note that recent advances in the generation of homoenolates directly from enals by nucleophilic heterocyclic carbene (NHC) catalysis also provides a facile entry to a homoenolate intermediate.[5]

Though research into the development of different metal homoenolates (especially those of titanium and zinc homoenolates) has been studied to a certain extent, to the best of our knowledge, exploration on the synthesis of indium homoenolate has not been undertaken so far. Furthermore, previous research on metal homoenolates is mainly focused on carbonyl compounds of ester and amide rather than ketone, which might be due to the fact that a metal homoenolate (particularly titanium homoenolate) is so reactive that it spontaneously reacts with the ketone to generate the more stable cyclopropanol tautomer. In this regard, organoindium reagents exhibit better compatibility with functional groups such as ketone, aldehyde, and alcohol.[6,7] Therefore, it is still desirable to develop an efficient method for the synthesis of an indium homoenolate containing a carbonyl group (especially ketone) which is currently unavailable. Herein, we describe an efficient method for the synthesis of a water-tolerant, ketone-type indium homoenolate via oxidative addition of indium(I) reagent to enone in aqueous media.[8,9] The synthetic utility of the indium homoenolate was demonstrated by the synthesis of 1,4-dicarbonyl compounds via palladium-catalyzed coupling with acid chlorides.

In our attempts to develop the Umpolung chemistry of enone in water, we studied the reaction of ethyl vinyl ketone with aldehyde using our previously developed system of In/CuI/$InCl_3$[10] in THF/H_2O. In addition to obtaining the β,γ-unsaturated ketone product,[11,12] we also isolated a relatively polar byproduct by silica gel column chromatography. NMR spectroscopy showed that the oil byproduct was only a saturated derivative of ethyl vinyl ketone (four sets of peaks between 0−5 ppm in ^{1}H NMR) and has an abnormal CH_2 located at 0.83 ppm (t, $J = 7.16$ Hz) in the ^{1}H NMR and at 8.4 ppm in the ^{13}C NMR (see the Supporting Information for details). We hypothesized that it might be an organoindium complex, and this information encouraged us to look further into the byproduct. In order to determine the structure, we were able to obtain a crystal of the organoindium complex suitable for X-ray diffraction analysis when phenyl vinyl ketone was used as a substrate and subjected to an analogous reaction system as above (In/$InCl_3$, CH_3CN/H_2O). X-ray diffraction analysis proved that the product is a phenyl substituted indium homoenolate, having a monomeric structure with chelation of the two carbonyl groups to indium (Figure 1). The coordination conformation of the central metal can be described as a distorted trigonal bipyramid, in which C(9), C(18), and Cl(1) are considered to occupy the equatorial plane and O(1) and O(2) occupy the apical positions. The average C═O bond length of 1.232 Å is in accordance with that in titanium homoenolate (1.235 Å)[2j] but is smaller than the C−O bond length in the enal-derived allylnickel complex.[9a] The average C−C bond lengths (1.529 Å) which are adjacent to the In−C bonds is slightly larger than those in the titanium analogue (1.503 Å).[2j]

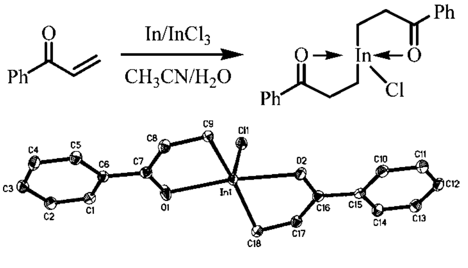

Figure 1. X-ray crystal structure of phenyl substituted indium homoenolate (CCDC 776440). Selected bond lengths (Å) and angles (deg): In(1)−C(9) 2.141(6), In(1)−C(18) 2.174(6), In(1)−O(1) 2.431(7), In(1)−O(2) 2.413(5), O(1)−C(7) 1.236(6), O(2)−C(16) 1.227(5), C(8)−C(9) 1.525(5), C(17)−C(18) 1.532(6); C(9)−In(1)−O(1) 78.1(2), C(18)−In(1)−O(2) 75.1(2), O(2)−In(1)−O(1) 168.7(3).

It is interesting to note that the indium homoenolate can be generated in aqueous media. In other words, the indium homoeno-

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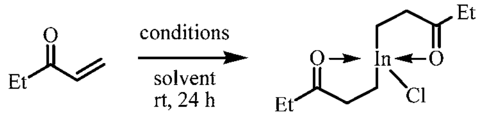
Table 1. Optimization of Reaction Conditions[a]



entry	conditions	yield (%)[b]
1	In (0.8 equiv)/$InCl_3$ (0.4 equiv), CH_3CN/H_2O	82 (90)[c]
2	In (1.2 equiv), CH_3CN/H_2O	0
3	$InCl_3$ (1.2 equiv), CH_3CN/H_2O	0
4	InCl (1.2 equiv), CH_3CN/H_2O	81
5	$InCl_2$ (2.4 equiv), CH_3CN/H_2O	78
6	In (0.8 equiv)/$InCl_3$ (0.4 equiv), MeOH	56

[a] The reactions were carried out at room temperature for 24 h using ethyl vinyl ketone (2 mmol, 1 equiv). [b] Isolated yield. [c] On a 20 mmol scale.

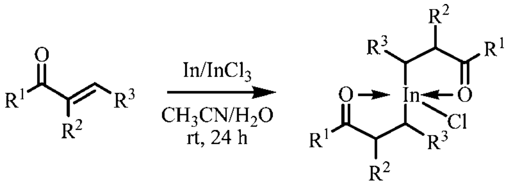
late is tolerant to water, and currently there are only a few reports related to the finding of water-tolerant organoindium complexes (mainly allylic indium species).[13] It was found that the indium homoenolate is not sensitive to acid too. Though it decomposes very slowly at room temperature, it can be stored at −80 °C without decomposition.

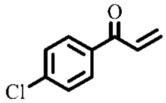
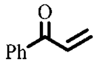
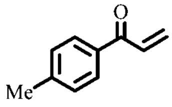
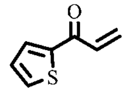
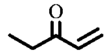
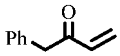
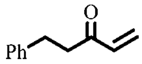
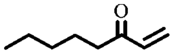
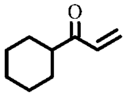
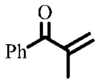
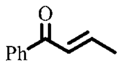
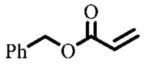
Preliminary studies were carried out to optimize the yield of the indium homoenolate using ethyl vinyl ketone as a substrate, and the results are summarized in Table 1. As shown in Table 1, the indium complex could be isolated in 82% yield when the reaction was performed in CH_3CN/H_2O for 24 h using 0.8 equiv of indium and 0.4 equiv of indium(III) chloride (entry 1).[14] It is important to note that both indium and indium(III) chloride are necessary for the efficient transformation of the enone to the corresponding indium homoenolate. Without either indium or indium(III) chloride, the reaction did not occur (Table 1, entries 2 and 3). Considering that 0.8 equiv of indium and 0.4 equiv of indium(III) chloride are equivalent to 1.2 equiv of indium(I) chloride ($2In + InCl_3 \leftrightarrow 3InCl$), we hypothesized that the real indium species which effects the transformation might be an indium(I) chloride. When performing the above reaction using InCl as a reaction mediator, we were pleased to observe that the reaction also took place in the presence of InCl (1.2 equiv) or $InCl_2$ (2.4 equiv), affording the desired products in good yields of 81% and 78%, respectively (Table 1, entries 4 and 5, and also refer to the Supporting Information for the two equations which account for the theoretical amount of $InCl_x$ which should be used in the reaction).

Based on the fact that the α-position of the enone should be protonated by H_2O to generate the final indium homoenolate, it was easy to rationalize the need of water. Screening of the reaction in other organic solvents further revealed that water is indispensable for the efficient progress of the reaction. No reaction occurred in pure organic solvents such as THF, CH_2Cl_2, EtOAc, and CH_3CN. It is worthwhile to note that a moderate yield was obtained when the same reaction was carried out in MeOH because it also can serve as a proton source for protonation of the indium homoenolate anion (Table 1, entry 6).

With the optimized reaction conditions in hand, a variety of enones were used as substrates to investigate the general applicability of the method for the preparation of indium homoenolates. As shown in Table 2, in most cases, moderate to good yields of the desired products were obtained. Aromatic enones with either electron-withdrawing or electron-donating groups reacted well under the optimized conditions (Table 2, entries 1−3). Enone with a heteroaromatic substituent also could be effectively converted (Table 2, entry 4). Aliphatic enones also served as reactive substrates for the reactions, affording the desired products in moderate to good yields (Table 2, entries 5−9). Notably, an enone with a methyl group incorporated at the α-position also worked well under this condition to give the product in good yield (Table 2, entry 10). Unfortunately, no product was obtained when β-substituted enone or α,β-unsaturated ester was used as the substrate (Table 2, entries 11−12).

Table 2. Substrate Scope Studies[a]

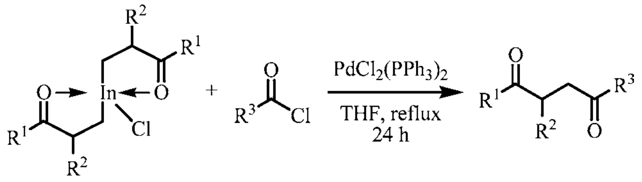


entry	substrate	product	yield (%)[b]
1		**1a**	75
2		**1b**	53
3		**1c**	89
4		**1d**	81
5		**1e**	82
6		**1f**	59
7		**1g**	90
8		**1h**	83
9		**1i**	82
10		**1j**	74
11		--	0
12		--	0

[a] The reactions were carried out at rt for 24 h using indium (1.6 mmol), indium(III) chloride (0.8 mmol), and enone (2 mmol) in CH_3CN/H_2O (5 mL/5 mL). [b] Isolated yield.

The synthetic utility of the indium homoenolate was demonstrated by subjecting it to acid chloride in the presence of a palladium catalyst to afford 1,4-dicarbonyl compounds (Table 3).[15−17] As shown in Table 3, in all cases, the coupling reactions proceeded efficiently in the presence of $PdCl_2(PPh_3)_2$ in THF to afford the desired products in moderate to good yields. Aromatic acid chlorides with electron-withdrawing or electron-donating groups reacted well. Acid chlorides with a heteroaromatic substituent also could be effectively transformed (Table 3, entries 8−9). In addition, aliphatic acid chlorides also worked well under the optimized conditions, though moderate yields were obtained (Table

Table 3. Palladium-Catalyzed Coupling of Indium Homoenolates with Various Acid Chlorides[a]



entry	R^1	R^2	R^3	product	yield (%)[b]
1	Et	H	4-$NO_2C_6H_4$	**2a**	84
2	Et	H	4-BrC_6H_4	**2b**	61[c]
3	Et	H	4-ClC_6H_4	**2c**	84
4	Et	H	Ph	**2d**	83
5	Et	H	4-MeC_6H_4	**2e**	87
6	Et	H	4-$OMeC_6H_4$	**2f**	74
7	Et	H	2-naphthyl	**2g**	89
8	Et	H	2-thienyl	**2h**	90
9	Et	H	2-furyl	**2i**	98
10	Et	H	$PhCH_2CH_2$	**2j**	69
11	Et	H	$PhCH_2$	**2k**	64
12	4-ClC_6H_4	H	4-MeC_6H_4	**2l**	78
13	Ph	H	4-MeC_6H_4	**2m**	70
14	4-MeC_6H_4	H	4-MeC_6H_4	**2n**	86
15	2-thienyl	H	4-MeC_6H_4	**2o**	85
16	$PhCH_2$	H	4-MeC_6H_4	**2p**	79
17	$PhCH_2CH_2$	H	4-MeC_6H_4	**2q**	84
18	*n*-pentyl	H	4-MeC_6H_4	**2r**	98
19	*c*-hexyl	H	4-MeC_6H_4	**2s**	70
20	Ph	Me	4-MeC_6H_4	**2t**	85

[a] The reactions were carried out at reflux for 24 h using indium homoenolate (0.3 mmol), acid chloride (0.5 mmol), and $PdCl_2(PPh_3)_2$ (0.025 mmol) in THF (3 mL). [b] Isolated yield based on acid chloride as limiting reagent. [c] With ~5% impurity which cannot be purified.

3, entries 10−11). Moreover, the reactions of various indium homoenolates with 4-methylbenzoyl chloride proceeded efficiently to give the final products in good yields (Table 3, entries 12−20). Finally, it is important to note that both of the two R groups attached to the indium (R_2InCl) can be efficiently transferred in the palladium-catalyzed coupling with acid chloride.

In summary, a novel method for the synthesis of the first indium homoenolate was achieved via the oxidative addition of InCl (or $In/InCl_3$) to enones in aqueous media. The indium homoenolate was found to be water-tolerant and represents one of the few already discovered organoindium complexes. The structure of one of the indium homoenolates has been confirmed by single crystal X-ray analysis. The method also provides an easy access to the synthesis of a carbonyl-containing organoindium reagent and ketone-type homoenolate which are not readily available by conventional methods. The synthetic utility of the indium homoenolate was demonstrated through the synthesis of 1,4-dicarbonyl compounds via palladium-catalyzed coupling with acid chloride. It is important to note that 1,4-dicarbonyl compounds are important intermediates in organic synthesis which are difficult to construct using conventional methods.[15] The transformation of the enone to indium homoenolate also represents one of the few Umpolung chemistries of enone with inversion of its β-carbon polarity. Further studies concerning other methods for the synthesis of indium homoenolates and their synthetic utility in organic synthesis are currently in progress.

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Supporting Information Available: Experiment procedures, characterization data of products, copies of ^1H and ^{13}C NMR spectra, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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