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Indium(III)-catalysed highly regioselective addition of thiolacetic acid to non-activated olefins

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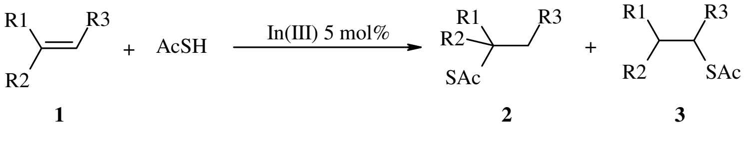
Abstract—Indium(III) chloride and indium(III) trifluoromethanesulfonate were found to be excellent catalysts for the addition of thiolacetic acid to non-activated olefins. The reaction is highly regioselective and can be run in the presence of 1 mol % of catalyst.

In the last few years, indium derivatives and particularly indium(III) chloride and trifluoromethanesulfonate have found successful applications as catalysts in synthetic organic chemistry, for example, in ring opening of epoxides and aziridines,[1] Mukaiyama-type reactions,[2] intramolecular Prins-type cyclisations,[3] Diels–Alder cycloadditions,[4] reductive Friedel–Crafts alkylations[5] or thioacetalisation of aldehydes and ketones.[6] Moreover, $InCl_3$ and $In(OTf)_3$ are stable under air and in water and constitute interesting catalysts for clean and green chemistry, due to the possibility of recovery and recycling.[7]

Sulfur compounds constitute an interesting family of natural compounds in particular in the field of flavour and fragrance chemistry.[8] Although present in trace amounts, they often play an important role in the overall aroma of coffee, meat, vegetables and fruits.[9] Thiols are known to be among the most powerful sulfur compounds from the point of view of their organoleptic properties. Their synthesis usually involves the functionalisation of an olefin with hydrogen sulfide or thiolacetic acid, followed by the thioester reduction to the thiol. The olefin addition is generally carried out in the presence of a radical initiator such as AIBN,[10] UV irradiation,[11] or an oxidising agent[12] promoting the formation of sulfur centered radicals and anti-Markovnikov-type adducts. It can also be carried out in acidic media and an heterogeneous system based on Montmorillonite K10 clay has been reported for the addition of thiobenzoic acid to olefins.[13] Although several examples report the addition of thiolacetic acid to conjugated olefins in a Michael-type reaction in basic media,[14] to our knowledge, there is no example of a catalytic system involving the use of Lewis acids to effect the addition of thiolacetic acid to non-activated olefins.

In the aim to develop a new system involving Lewis acid catalysis for the functionalisation of alkenes, we examined the indium(III)-catalysed addition of thiolacetic acid to non-activated olefins (Scheme 1).



Scheme 1.

Keywords: Indium chloride; Indium triflate; Markovnikov-type addition; Thiolacetic acid; Non-activated olefins.

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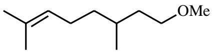
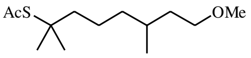
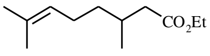
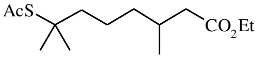
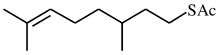
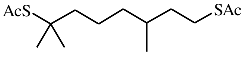
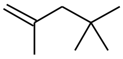
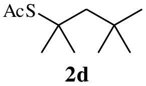
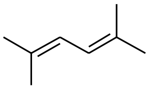
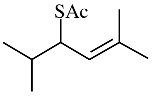
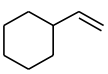
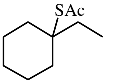
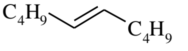
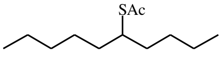
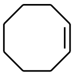
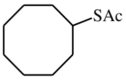
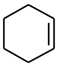
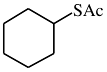
The efficiency of several metallic triflates was tested for the addition of AcSH to citronellyl methyl ether **1a** (See Table 1) chosen as the model compound.

The use of strong Lewis acids such as $Al(OTf)_3$ or $Sc(OTf)_3$ in 5 mol % ratio led regioselectively to **2a** though in a slow reaction (10 h in refluxing 1,2-dichloroethane). In contrast, $InCl_3$ or $In(OTf)_3$ showed high catalytic activity with the clean and regiospecific formation of thioacetate **2a** in less than 1 h. The reaction could also be run in the presence of 1 mol % In(III) catalyst without solvent and **2a** was obtained in 92% yield after 24 h. Under the different conditions, either $In(OTf)_3$ or $InCl_3$ afforded regiospecifically the thioacid addition on the most substituted site of the olefin, in a Markovnikov-type addition. It is noteworthy that the regiochemical outcome is the opposite to that obtained by the more classical radical-type addition with AIBN.[10]

The In(III)-catalysed selective functionalisation of C–C double bonds was further extended to other differently substituted olefins. The results are summarised in Table 1. Several trisubstituted olefins **1a**–**c** (entries 1–3) were selectively converted into the corresponding thioacetates **2** (Markovnikov product) in almost quantitative yields. 2,2-Disubstituted alkene **1d** afforded regiospecifically the AcS– addition into the 2-position of the double bond to afford **2d** as the single isomer in 86% isolated yield (entry 4). Conjugated diene **1e** (entry 5) was also regioselectively converted into the monothioacetate **2e**. Only one AcS– group was incorporated into the 1,3-diene, regardless of the excess of thiolacetic acid.

For mono- and 1,2-disubstituted olefins **1f**–**i** (entries 6–9), indium(III) chloride was less efficient and afforded low conversions. However, $In(OTf)_3$ showed a good catalytic activity for the addition of AcSH to these less substituted double bonds, in particular in refluxing nitromethane (entries 7 and 8), a more polar and higher boiling point solvent. For terminal olefin **1f**, the expected thioacetate issued from the addition of the AcS– moiety to the internal olefinic carbon did not occur. Instead, the reaction led cleanly to **2f** in 91% isolated yield. Thioacetate **2f** results from a first

Table 1. In(III)-catalysed thioacetylation of olefins[15]

Entry	Substrate	Conditions	Product	% Yield regioselectivity (**2**/**3**)
1	 **1a**	$InCl_3$ (5 mol %) $ClCH_2CH_2Cl$ 80 °C, 1 h	 **2a**	87 (100/—)
2	 **1b**	$InCl_3$ (5 mol %) $ClCH_2CH_2Cl$ 80 °C, 1 h	 **2b**	92 (100/—)
3	 **1c**	$InCl_3$ (5 mol %) $ClCH_2CH_2Cl$ 80 °C, 1 h	 **2c**	93 (100/—)
4	 **1d**	$InCl_3$ (5 mol %) $ClCH_2CH_2Cl$ 80 °C, 0.5 h	 **2d**	86 (100/—)
5	 **1e**	$InCl_3$ (5 mol %) $ClCH_2CH_2Cl$ 80 °C, 0.25 h	 **2e**	92 (100/—)
6	 **1f**	$In(OTf)_3$ (5 mol %) $ClCH_2CH_2Cl$ 80 °C, 2 h	 **2f**	91
7	 **1g**	$In(OTf)_3$ (5 mol %) CH_3NO_2 100 °C, 15 h	 **2g** and isomers	72
8	 **1h**	$In(OTf)_3$ (5 mol %) CH_3NO_2 100 °C, 2 h	 **2h**	70
9	 **1i**	$In(OTf)_3$ (1 mol %) no solvent 80 °C, 48 h	 **2i**	67

isomerisation of the double bond followed by the addition of thiolacetic acid on the *tertiary* carbon. For comparison, with the use of 5 mol % $InCl_3$, **2f** was also formed as the only product, but in 60% yield after 72 h. A strong counter-ion effect was observed for this reaction.

For linear alkene **1g**, an isomerisation of the double bond through the alkyl chain occurred and a mixture of the four thioacetate isomers was obtained in 72% overall yield. Thioacetylation of cyclooctene **1h** and cyclohexene **1i** was efficiently catalysed by $In(OTf)_3$ to afford the corresponding derivatives **2h** and **2i**, respectively. The functionalisation of **1i** could be run without solvent in the presence of 1 mol % $In(OTf)_3$, affording cyclohexanyl thioacetate **2i** in 67% yield.

The observed Markovnikov-type regioselectivity as well as the isomerisation of the double bond for substrates **1f** and **1g** indicated that the mechanism most probably involves a protic pathway. Moreover, a reaction with olefin **1d** under the conditions of entry 4 with added 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 5 mol %) as a hindered base led to no thioacid addition after 0.5 h. After 10 h, some addition occurred with completely reversed regioselectivity, in an anti-Markovnikov reaction, most probably due to a slow radical-type reaction with light. We propose that the In(III) catalyst forms an In(III) thioacetate and liberates H^+, responsible for the catalytic activity. The formation of an intermediate In(III) thioacetate may enhance the acidity of AcSH as well as the nucleophilicity of the thioacetate moiety. This catalytic system constitutes a novel example of the newly reported Lewis acid-assisted Brønsted acid catalysed process.[16]

In conclusion, $InCl_3$ and $In(OTf)_3$ were shown for the first time to be very efficient catalysts for the regiospecific Markovnikov-type addition of thiolacetic acid to non-activated olefins. The reaction was carried out without solvent and in the presence of 1 mol % In(III) for the functionalisation of substrates **1a** and **1i**. $InCl_3$ is an efficient catalyst for the addition of thiolacetic acid to trisubstituted olefins, and the use of more active $In(OTf)_3$ is required for the addition to mono- and disubstituted olefins. The In(III)-catalysed selective isomerisation of C–C double bonds to more substituted olefins occurred in some cases.

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15. General procedure for the In(III)-catalysed addition of thiolacetic acid to olefins: to a mixture of olefin (5 mmol) and $InCl_3$ or $In(OTf)_3$ (5 mol %) in distilled 1,2-dichloroethane (5 mL) was slowly added thiolacetic acid (5.5 mmol). The temperature was increased to 80 °C and the progress of the reaction was monitored by GC analysis. On completion of the reaction, the mixture was quenched with HCl 1 M and extracted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$ and dried with $MgSO_4$. The solvent was evaporated and the products were purified and analysed by ^1H and ^{13}C NMR and mass spectrometry.
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