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Indium-mediated, highly efficient cyclopropanation of olefins using CH_2I_2 as methylene transfer reagent

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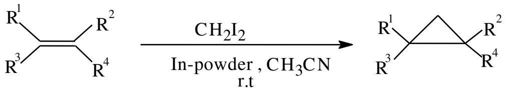
Abstract—The indium-mediated, one-pot cyclopropanation of a variety of olefins with methylene iodide proceeds smoothly with excellent yields of products.

Organometallic reactions involving the direct use of a metal are of current interest as they avoid the use of sensitive, toxic and expensive organometallics.[1] In recent years increasing emphasis has been placed on the development of indium-mediated organic transformations because of indium's unique properties, such as stability towards air and moisture, its nontoxic nature and its availability in pure form.[2] This has led to the widespread use of indium in Barbier Grignard-type,[3] Reformatsky[4] and carbonyl addition reactions.[5]

The cyclopropanation of olefins is an important synthetic transformation as cyclopropane rings are present in a variety of naturally occurring compounds and can undergo a plethora of reactions.[6] The Simmons–Smith reaction[7] and several of its modifications[8] involving methylene transfer using carbenoid species have proved to be powerful tools for the synthesis of cyclopropanes, however, these methods suffer from several drawbacks such as harsh reaction conditions and long reaction times due to the low reactivity of zinc, metal. Besides zinc other metals such as samarium[9] and aluminium alkyls[10] have been used for methylene transfer reactions, but the moisture sensitivity of samarium and the pyrophoric nature of aluminium alkyls make these methods less attractive. To the best of our knowledge there is no literature report on the cyclopropanation of olefins involving methylene transfer mediated by indium. In continuation of our studies on metal-based synthetic transformations,[11] herein, we report a novel, one-pot, highly efficient indium-mediated cyclopropanation of olefins under very mild conditions using methylene iodide as the methylene transfer reagent (Scheme 1).



Scheme 1.

The reaction of a variety of olefins with one equivalent of methylene iodide and indium in acetonitrile resulted in the formation of the corresponding cyclopropanes at room temperature.[12] The results of these experiments are presented in Table 1. Among the various olefins studied, alicyclic olefins were found to be most reactive (Table 1, entries f–h). Similarly aromatic substituted olefins possessing electron donating groups (Table 1, entries b–c) were found to be reactive. It was interesting to note that dropwise addition of methylene iodide gave better yields of the cyclopropanes. When the indium-mediated cyclopropanation of 4-methylstyrene was carried out using methylene chloride as the methylene transfer reagent, no cyclopropanation product was observed. Cyclopropanation of 4-methylstyrene was carried out in various solvents including THF, diethyl ether, acetonitrile and toluene to evaluate the solvent effect and acetonitrile was found to be the most suitable

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Keywords: Cyclopropanation; Methylene transfer; Indium; Olefins; Methylene iodide.

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Table 1. Indium-mediated cyclopropanation of olefins with methylene iodide[a]

Entry	Olefin	Reaction time (h)	Yield (%)[b]
a	Styrene	5.5	80
b	4-Methylstyrene	5.0	85
c	3-Methylstyrene	5.5	80
d	α-Methylstyrene	4.0	87
e	Methyl methacrylate	3.75	85
f	Cycloheptene	1.5	88
g	Cyclohexene	1.75	92
h	Cyclopentene	2.5	90
i	4-Vinylanisole	5.0	76
j	4-Chlorostyrene	8.0	65
k	*trans*-Methyl cinnamate	7.5	50

[a] Reaction conditions: olefin (1 mmol), indium powder (1 mmol), methylene iodide (1.2 mmol), acetonitrile (5 ml) at room temperature under a nitrogen atmosphere.

[b] Isolated yields.

for this reaction from the point of view of yields. The mechanism of the reaction is not clear at this stage; the reaction probably involves the formation of an organoindium-halide species by the reaction of methylene iodide and metallic indium[13] followed by its reaction with the olefin to yield the cyclopropane.

In conclusion, we have described a new and highly efficient indium-mediated cyclopropanation of olefins in very good yields under mild conditions.

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12. *Typical experimental procedure*: To a stirred mixture of cyclohexene (82 mg, 1 mmol) and indium metal (114 mg, 1 mmol) in acetonitrile (5 ml) was added methylene iodide (320 mg, 1.2 mmol) drop by drop under a nitrogen atmosphere at 25 °C. Stirring was continued until the reaction mixture appeared turbid. After completion, the reaction mixture was filtered followed by evaporation of the solvent. The residue obtained was purified by passing through a short silica gel column using hexane/ethyl acetate (4:1) as eluent. Evaporation of the solvent yielded bicyclo[4.1.0]heptane (86 mg, 92%). Other cyclopropanes were prepared similarly, their reaction times and yields are presented in the Table 1.
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