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LETTERS

Indium-mediated carbonyl alkynylation

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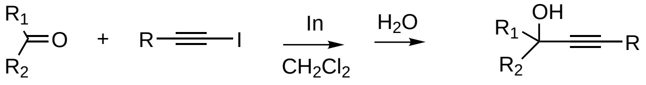
Abstract—Indium mediates a Barbier-type reaction between alkynyl halides and aldehydes or ketones to give secondary or tertiary propargyl alcohols. Secondary alcohols can be oxidised in situ according an Oppenauer process. © 2002 Elsevier Science Ltd. All rights reserved.

Barbier-type carbonyl alkylation mediated by indium is a well-known reaction involving generally allylic, propargylic or α-carbonyl halides.[1] We report herein Barbier-type reactions of alkynyl iodides with aldehydes or ketones mediated by indium powder (Scheme 1).

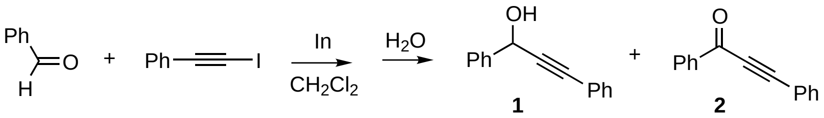
Relevant Barbier reactions were already described with chromium chloride in DMF[2] or samarium iodide in the presence of hexamethylphosphoric triamide.[3] Since indium is tolerant of water, we investigated first the reaction with aqueous solvents. In each case a reduction of the phenylalkynyl iodide used as the model was obtained, which prompted us to study the reaction in conventional organic solvents. The best yields were obtained with dichloromethane at reflux but a mixture of the propargyl alcohol **1** and the ketone **2** was observed (Scheme 2).



Scheme 1.

We have then formulated the hypothesis that the ketone **2** came from the Oppenauer oxidation of the transient indium alkoxide (corresponding to the alcohol **1)** with the subsequent reduction of benzaldehyde into benzylic alcohol. Such an oxidation during an alkynylation process was formally mentioned with vanadium acetylides.[4] The results presented in Table 1 confirmed this hypothesis. The increase of the molar amount of benzaldehyde allowed us to force the Oppenauer oxidation, whereas an excess of phenylalkynyl iodide prevented the oxidation (Table 1).

In a typical experiment to produce exclusively propargylic alcohol, indium powder (138 mg, 1.2 mmol) was placed in a Schlenk tube under argon, followed by the addition of dichloromethane (6 mL) and phenylalkenyl iodide (228 mg, 1 mmol) and then benzaldehyde (53 mg, 0.5 mmol). The heterogeneous mixture was stirred at reflux for 24 h. The reaction was quenched with a sodium bicarbonate aqueous solution. The product was extracted with ether, washed with brine, dried with anhydrous Mg_2SO_4, concentrated under reduced pressure, and separated with silica gel chromatography using a mixture of cyclohexane and ethyl acetate as the eluent, affording 1,3-diphenylprop-2-ynol in 83% yield.



Scheme 2.

Keywords: indium; alkynylation; propargyl alcohol; Barbier reaction; Oppenauer oxidation.

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Table 1. Indium-mediated alkynylation of phenylalkynyl iodide with benzaldehyde

Iodide (equiv.)	PhCHO (equiv.)	In (equiv.)	Time (h)	Yield of **1** (%)	Yield of **2** (%)
1	1.2	1.2	24	42	38
1	2	1.2	24	35	65
1	3	1.2	48		44
2	1	1.2	24	70	Trace
2	1	2.4	24	83	Trace

Table 2. Indium-mediated alkynylation of alkynyl iodide with carbonyl compounds[a]

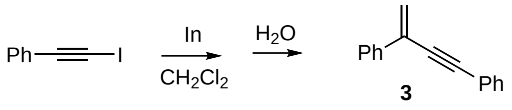
Run	Alkynyl iodide R	Carbonyl compound R_1, R_2	Time (h)	Yield (%)
1	Ph	Ph, H	24	83
2	Ph	$CH_3(CH_2)_6$, H	24	87
3	Ph	$CH_3(CH_2)_2$, H	24	90
4	Ph	C_6H_4-*p*CH_3, H	24	70
5	Ph	C_6H_4-*p*CF_3, H	24	78
6	Ph	C_6H_4-*p*NMe_2, H	24	25
7	Ph	Naphtyl, H	24	0
8	Ph	Anthryl, H	24	0
9	Ph	$PhCH(CH_3)$, H	24	89[b]
10	Ph	Tbu	24	96
11	Ph	C_6H_{11}, H	24	99
12	Ph	PhCH=CH, H	24	0
13	Ph	CH_3CH=CH, H	24	0
14	Ph	-$(CH_2)_5$-	24	94
15	Ph	-$(CH_2)_4$-	24	85
16	Ph	CH_3CH_2, CH_3CH_2	24	89
17	Ph	$(CH_3)_2CH$, $(CH_3)_2CH$	24	72
18	Ph	Ph, Ph	24	0
19	Ph	Ph, CH_3	24	33
20	$CH_3(CH_2)_3$	Ph, H	7	83
21	$CH_3(CH_2)_3$	C_6H_{11}, H	7	90
22	$CH_3(CH_2)_3$	Ph, CH_3	24	26
23	$CH_3(CH_2)_3$	-$(CH_2)_5$-	11	97

[a] Alkynyl iodide (2 equiv.), In (2.4 equiv. with aldehyde, 1.8 equiv. with ketone), reflux of dichloromethane.

[b] diastereomeric excess: 30%.

The reaction was tested with various aldehydes under the same conditions (Table 2, runs 1–13) and with another alkynyl iodide (Table 2, runs 20–23). The yield in propargylic alcohol was generally high except for unsaturated aldehydes. In the case of anthraldehyde (run 8), we detected the formation of the oxidation product (20%) of the expected propargylic alcohol. For such an aldehyde the Oppenauer oxidation was certainly more rapid than the preceding alkynylation; this is probably due to the π-stacking of the reactants facilitating the hydride transfer between them.

The alkynylation reaction of ketones was generally slower than the same reaction with aldehydes. Owing to a competitive coupling leading to the enyne **3**, an excess of alkynyl iodide was necessary to get a good yield; 2 equiv. of alkynyl iodide was therefore engaged in the reaction which proceeded nicely except with aromatic ketones for the previously invoked reason (Table 2). The formation of the enyne **3**, which was independently achieved with indium and phenylalkenyl iodide in dichloromethane at reflux (Scheme 3), is due to a carboindation of carbon–carbon bonds which is reminiscent of a relevant reaction with allyl- and benzylindium reagents.[5]



Scheme 3.

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