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Indium-mediated highly regioselective reaction of prop-2-ynyl bromides with acyl cyanides in aqueous media: a convenient synthesis of allenic and propargylic ketones

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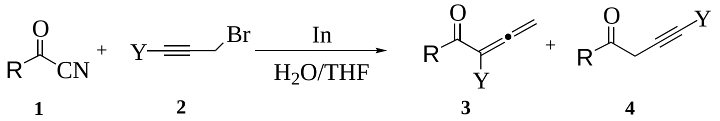
Abstract—Indium-mediated reaction of acyl cyanides **1** with prop-2-ynyl bromides **2** in aqueous media occurs regioselectively to afford either allenic **3** or propargylic ketones **4** depending on the γ-substituent of the prop-2-ynyl bromide under the mild conditions. © 2001 Elsevier Science Ltd. All rights reserved.

The development of organometallic-type reactions in aqueous media is of current interest because they offer the possibility of environmentally benign reaction conditions.[1] Particularly, indium-mediated reactions in aqueous media have recently attracted considerable attention in organic synthesis over the last decade.[2] Relative to allylation, much less attention has been paid to the reaction of carbonyl compounds with propargyl bromide and indium. It has recently been reported that indium-mediated propargylation and allenylation of a variety of carbonyl compounds give either homopropargylic alcohols or allenic alcohols.[3] However, the indium-mediated propargylation of carboxylic acid derivatives has not been well studied. Allenyl and propargyl metal derivatives are of particular interest since they equilibrate in solution in many cases.[4] This metallotropic rearrangement often results in poor regioselection in the final organic product, because both organometallic species can react differently with the carbonyl compounds. Allenic and propargylic ketones are valuable substrates for a variety of synthetic targets in organic chemistry, but relatively few methods have been employed for their preparation.[5] Those methods frequently result in a mixture of isomers (**3** and **4**) and was thus synthetically not too useful. We have found that acyl cyanide can act as an electrophile in the indium-mediated propargylation or allenylation to give the corresponding propargylic or allenic ketones in good yields (Scheme 1). Recently, we have found that the reaction of acyl cyanides with allyl bromides in aqueous media was successfully carried out to afford β,γ-unsaturated ketones.[6] To the best of our knowledge the indium-mediated propargylation or allenylation has never been applied to acyl cyanides. We now wish to report our study on the regioselective synthesis of allenic ketones and propargylic ketones mediated by indium using acyl cyanide as substrate in aqueous media. For the reaction is carried out in aqueous



2a Y = H
2b Y = Me
2c Y = Ph

Scheme 1.

Keywords: propargylation; allenylation; acyl cyanides; indium and compounds.

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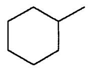
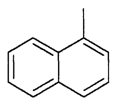
tetrahydrofuran solution and in the air, the procedure is simple and convenient.[7] In the reactions, substituents such as methoxy, chloro, or bromo groups on aromatic rings remained unaffected (entries 2, 3, 8 and 9). As one can see from the results in Table 1, the reaction was found to be general being applicable to aromatic, aliphatic acyl cyanides. All the compounds obtained showed IR, NMR and mass spectral data compatible with the structure.[8] With the parent prop-2-ynyl bromide, indium-mediated coupling with aliphatic or aromatic acyl cyanides in aqueous media gave mainly the allenic ketones **3** in good yields. In contrast, when the prop-2-ynyl bromide is γ-substituted, the coupling products were exclusively the propargylic ketones **4**. For related indium-mediated reactions, regioselectivity has been proposed to be controlled by both steric and electronic effects.[9] The organoindiums act as ambident nucleophiles and the acetylene/allene distribution appears to be influenced by the steric property of the propargyl bromide. Presumably the regiochemistry obtained in the present case is highly dependent on steric hindrance and thus a substituent in the organoindium compounds enhances the formation of acetylenic ketones **4**.

In conclusion, we have discovered that the present procedure provides a simple and convenient method for the regioselective synthesis of propargylic and allenic ketones in aqueous media under the mild conditions. We believe this will make a useful and important addition to the existing methods and will find practical applications in organic synthesis. Further studies to develop other new reactions using indium in aqueous media are currently in progress.

Table 1. Indium-mediated coupling of propargyl bromides with acyl cyanides

Entry	Acyl cyanide **1**	Propargyl bromides **2**	Yield (%)[a]	
	R	Y	**3**	**4**
1	Ph	H	69	–
		Me	–	73
		Ph	–	83
2	4-$CH_3OC_6H_4$	H	75	–
		Me	–	67
		Ph	–	81
3	2-ClC_6H_4	H	73	–
		Me	–	76
		Ph	–	67
4	$CH_3(CH_2)_8$	H	81	–
		Me	–	87
		Ph	–	57
5	4-$CH_3C_6H_4$	H	73	–
6	2-$CH_3C_6H_4$	H	75	–
7	4-*t*-BuC_6H_4	H	73	–
8	2-BrC_6H_4	H	63	–
9	4-BrC_6H_4	H	67	–
10		H	73	–
11		H	69	–

[a] Isolated yields.

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7. *Representative experimental procedure*: Indium metal powder (137 mg, 1.20 mmol) was added to a stirred solution of prop-2-ynyl bromides (152 mg, mmol) in water (5 mL) and the stirring was continued for 30 min at room temperature. Acyl cyanide (1 mmol) in THF (1 mL) was then added dropwise. The resulting mixture was stirred at room temperature for 1 h and the progress of the reaction was monitored by TLC. The reaction was quenched with dilute

sodium hydroxide (1N) and extracted with ethyl acetate. Evaporation of the solvent followed by purification via silica gel chromatography gave allenic ketone **3** (92.1 mg, 69%).

8. Typical physical data of representative compounds. Entry 1 in Table 1: Compound **2a** (**1-phenylbuta-2,3-dien-1-one**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, 2H, $J=7.4$ Hz), 7.54 (br t, 2H), 7.43 (m, 1H), 6.44 (t, 1H, $J=6.5$ Hz), 5.26 (d, 1H, $J=6.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.5, 191.5, 137.9, 133.2, 129.1, 128.8, 93.7, 79.7; GC–MS m/z: 144 (M^+). Compound **2b** (**1-phenylpent-3-yn-1-one**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 2H, $J=8.4$ Hz), 7.47 (m, 1H), 7.38 (m, 2H), 5.02 (s, 2H), 2.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.4, 138.1, 131.9, 129.0, 127.7, 101.9, 78.3, 29.7, 14.7; GC–MS m/z: 158 (M^+).
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