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Indium-mediated coupling of bromoacetonitriles with aromatic acyl cyanides: convenient synthesis of aromatic α-cyano ketones

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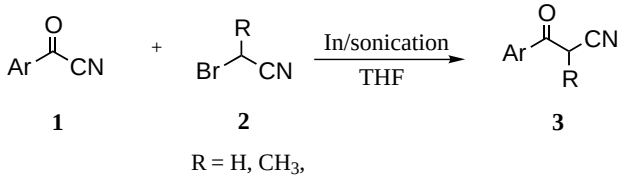
Abstract—Indium-mediated coupling of bromoacetonitrile and 2-bromopropionitrile with a variety of aromatic acyl cyanides afforded the corresponding aromatic α-cyano ketones in moderate to good yields under mild and neutral conditions.

Indium-mediated reaction is one of the attractive synthetic methods for a carbon–carbon bond formation[1] and has gained much attention over the last decade in a variety of reactions such as Reformatsky reactions,[2] allylation[3] and propargylation[4] reactions of carbonyl compounds, or aldimines,[5] coupling of carbonyl derivatives.[6] Recently, the α-halo-organoindium reagents formed from indium metal and Br_2CR_2 (R = CN, CO_2Et) have been successfully employed in the cyclopropanation of alkenes, and in the epoxidation of carbonyl compounds.[7] It was also reported that the indium(I) halide-mediated coupling reactions of dibromoacetonitrile and trichloroacetonitrile with carbonyl compounds provide β-hydroxy nitriles.[8] Relative to cyanomethylation of aldehydes and ketones, little attention has been paid to the coupling of carboxylic acid derivatives with bromoacetonitriles. To the best of our knowledge, the indium-mediated cyanomethylation has never been applied to carboxylic acid derivatives. We have found that the indium-mediated reaction of acyl cyanides **1** with bromoacetonitriles **2** provides various α-cyano ketones **3** (Scheme 1). The versatile synthetic utility of α-cyano ketones has been described in a number of publications devoted to their preparation and utilization.[9] A general method for α-cyano ketones is a Claisen-type condensation with an ester of nitrile (or an ester) containing an α-hydrogen. However, the majority of these procedures seemed somewhat cumbersome and the nature of the deprotonating agent may have a crucial influence on the selectivity and the yield of the reaction. For synthetic applications, the present procedure should prove to be more practical than existing methodologies, provided that the synthesis can be efficiently achieved under simple and mild conditions. We wish to report herein our study on the reaction of organoindium reagents derived from bromoacetonitrile with aromatic acyl cyanides to afford the corresponding α-cyano ketones. Generally, the reactions were clean and proceed efficiently in moderate to good yields at room temperature under sonication. The indium-mediated reactions of bromoacetonitrile and 2-bromopropionitrile with a series of aromatic acyl cyanides are summarized in Table 1. Acyl cyanides were prepared by the literature procedure.[10] Unfortunately, when the substrate is benzoyl chloride or benzoyl anhydride, the reaction results in a complex mixture under the same conditions. Although the mechanism of the reaction is still not clarified, it is assumed that the reaction of bromoacetonitrile with indium powder smoothly proceeds to form organoindium reagent, $(NCCHR)_3In_2Br_3$, which reacts with carbonyl compounds to give the corresponding α-cyano ketones. It was known that $(NCCHR)_3In_2Br_3$ did not react with benzaldehyde in



1 **2** **3**

R = H, CH_3,

Scheme 1.

Keywords: acyl cyanide; coupling; indium and compounds; cyano ketone.

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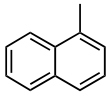
Table 1. Synthesis of aromatic α-cyano ketones mediated by indium

Entry	Acyl Cyanide **1** Ar	Bromoacetonitrile **2** R	Reaction Time (hr)	Yield(%)*
1	Ph	H	6	65
		CH_3	3	86
2	2-$CH_3C_6H_4$	H	12	66
		CH_3	4	77
3	4-$CH_3OC_6H_4$	H	7	71
		CH_3	3	79
4	2-ClC_6H_4	H	6	70
		CH_3	2	80
5	4-BrC_6H_4	H	5	72
		CH_3	3	81
6	2-BrC_6H_4	H	5	60
7	4-*t*-BuC_6H_4	H	6	80
8	4-$CH_3C_6H_4$	H	5	85
9		H	10	70
10		H	8	63
11	$CH_3(CH_2)_8$	H	12	0
12	Cyclohexyl	H	12	0

*Isolated yields.

the absence of additive such as chlorotrimethylsilane and the desired hydroxy nitrile product was not obtained at all.[11] However, in our study when acyl cyanide was chosen as a substrate, the reaction proceeded successfully without additives. It is noteworthy that practically no reaction occurred in the absence of sonication. The reaction was carried out in several solvents but failed in DMF, CH_3CN, THF/H_2O, DMF/H_2O and water. THF has been found to be the most suitable solvent for the reaction.[12] In the course of the process, substituents such as methoxy, chloro, and bromo groups on aromatic rings (entries 3–6) are not affected under the reaction condition. In order to assess the generality of the process, the reaction was studied with a variety of acyl cyanides. As shown in Table 1, the furfuroyl cyanide reacted with bromoacetonitrile to give the expected α-cyano ketone (entry 10), but the application of this method to aliphatic acyl cyanide proved unsuccessful and only recovered starting material was isolated (entries 11 and 12). 2-Bromopropionitrile reacts faster and produces better yields than bromoacetonitrile. All products obtained showed NMR, IR and mass spectral data compatible with the structure.

In conclusion, a mild and neutral preparation method for aromatic α-cyano ketones was achieved by the indium-mediated coupling of bromoacetonitrile and 2-bromopropionitrile with various aromatic acyl cyanides. We believe that this procedure will present a better and more practical alternative to the existing methodologies.

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12. Representative experimental procedure: Indium (517 mg, 4.5 mmol) was added to a stirred solution of bromoacetonitrile (720 mg, 6.0 mmol) in THF (10 mL) and the resulting mixture was stirred at room temperature for 1 h. To this solution was added dropwise a solution of benzoyl cyanide (393 mg, 3.0 mmol) in THF (1 mL) at room temperature. Stirring was continued for 6 h under sonication and the progress of the reaction was monitored by TLC. The reaction mixture was filtered through celite and extracted with ether. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:1) to afford benzoyl acetonitrile (283 mg, 65%).