

Indium-Mediated Addition of 4-Bromocrotonic Acid to Aldehydes and Ketones—A Simple, High Yielding Route to α -Allyl- β -Hydroxy Carboxylic Acids

Michael C. Bowyer,^A Charles M. Gordon,^B Sarah K. Leitch,^C Adam McCluskey,^{C,D} and Craig Ritchie^B

^A School of Applied Sciences, University of Newcastle, Ourimbah NSW 2258, Australia.

^B Department of Pure & Applied Chemistry, University of Strathclyde, Glasgow G1 1XL, UK.

^C Chemistry Building, School of Environmental & Life Sciences, University of Newcastle, Callaghan NSW 2308, Australia.

^D Author to whom correspondence should be addressed (e-mail: adam.mccluskey@newcastle.edu.au).

We report a simple procedure for the indium-mediated addition of 4-bromocrotonic acid to a variety of aldehydes and ketones. In all instances the reaction proceeds exclusively with α -addition and typically in moderate to good yields (42–100%). The effect of solvent is minimal allowing a wide choice of conditions (methanol, ethanol, ethanol/water, water, tetrahydrofuran, and the ionic liquid [bmIm][BF₄]).

Manuscript received: 27 August 2003.

Final version: 27 November 2003.

The allylation of carbonyl compounds to produce homoallylic alcohols has been described by several groups and is a synthetically significant transformation.^[1] The majority of such transformations are metal-mediated, with several metals suitable for such an approach.^[2] Over the past few years we have successfully developed, and reported the use of tetraallylstannane as one such species for a facile allylation of aldehydes, ketones, acetals (with silica or trifluoroacetic acid), and Weinreb amides.^[3] This reagent is more reactive and atom efficient than the trialkylstannane and dialkylallylstannane reagents often employed for allylation, as all four organic groups are transferred in the course of the reaction. More recently we have become aware of a significant limitation in this approach, that is, the lack of a succinct route to introduce additional functionality. Consequently, we turned our attention to the corresponding indium-mediated allylation. We,^[4] and others,^[5] have found that this approach is both convenient and efficient. From a green perspective, we have also demonstrated that the indium-mediated procedure is possible with catalytic quantities of indium (10%) and occurs readily in ionic liquids.^[4]

As a continuation of our previous studies, we were interested in further exploration of the indium-mediated allylation, but with a functionalized allyl bromide. Herein, we report our most recent development on the indium-mediated addition of 4-bromocrotonic acid to a variety of aldehydes and ketones.

Our initial experiments were designed to see if the indium-mediated allylation exhibited the same type of solvent dependency as did our original tetraallylstannane work.

Table 1. Allylation of benzaldehyde with 4-bromocrotonic acid using indium powder

Entry	Solvent	Conditions	Product conversion [%] ^A
1	MeOH	16 h, 30°C	83
2	MeOH	72 h, 30°C	95
3	MeOH	16 h, 30°C	94
4	H ₂ O	16 h, 30°C	84
5	EtOH/H ₂ O (20%)	72 h, 30°C	98
6	THF	72 h, 30°C	90
7	[bmIm][BF ₄] ^B	16 h, 50°C	64

^A Determined by ¹H NMR.

^B At the end of the reaction, the mixture was quenched with deionized water (2.5 mL).

Consequently, we investigated the effect of solvent (water to methanol to ionic liquids), of time and temperature (see Table 1). With the exception of the ionic liquid [bmIm][BF₄], all reactions proceeded with high conversion, and with no major discernable solvent or temperature dependence (Table 1, entries 1–6). In the case of [bmIm][BF₄] (entry 7), we believe the presence of serendipitous water is responsible for the efficient conversion noted.^[6] Of greater interest is the complete absence of the alternative addition product (Scheme 1). It is well known, for example from Loh's work,^[7] that indium-mediated allylations usually give rise to two adducts, α and γ , as indicated in Scheme 1. No γ -adduct was detected by ¹H NMR or GC-MS analysis (data not shown). This is also contrary to what we have observed with the addition of tetraallylstannanes, which

available materials. Our approach is highly regioselective facilitating the generation of only the α -adduct, and is tolerant of a range of solvents and reaction conditions.

Experimental

General Procedure for the Allylation of Carbonyl Compounds using Indium

4-Bromocrotonic acid (0.198 g, 1.2 mmol) and indium powder (Aldrich, 99.99% 100 mesh; 0.114 g, 1.0 mmol) were added to 2.5 mL of solvent (see Table 1) and stirred for a few minutes. The carbonyl compound (1 mmol) was then added, and the reaction vessel stoppered and the reaction mixture stirred at 30°C or 50°C for 16 h or 72 h. At the end of the reaction different methods were employed for the workup, as listed below.

Methanol: Remaining indium and indium hydroxide was removed by filtration through a cotton wool/kieselguhr plug, then the solvent was removed in vacuo.

Water: The products were extracted with diethyl ether (5 × 5 mL), the extracts were combined and dried (MgSO₄), then the solvent was removed in vacuo.

[bmIm][BF₄]: At the end of the reaction, the mixture was quenched with deionized water (3 mL). The water/ionic liquid mixture was then extracted with diethyl ether (5 × 5 mL), the extracts were combined and dried (MgSO₄), then the solvent was removed in vacuo.

Ethanol/water (20%): The products were extracted with diethyl ether (5 × 5 mL), the extracts were combined and dried (MgSO₄), then the solvent was removed in vacuo.

Tetrahydrofuran: At the end of the reaction, the mixture was quenched with deionized water (3 mL). The products were extracted with diethyl ether (5 × 5 mL), the extracts were combined and dried (MgSO₄), then the solvent was removed in vacuo.

Products were purified by flash chromatography (ethyl acetate/hexanes).

Representative Characterization Data

2-(Hydroxyphenylmethyl)-but-3-enoic acid: Yield 44–87%. δ_{H} (CDCl₃) 8.12 (1H, s, COOH), 5.94–5.88 (1H, q, CH(COOH)CHCH₂), 5.29–5.13 (2H, dd, *J* 10.2, 17.2, CHCH₂), 5.08–5.06 (1H, d, *J* 5.6, PhCH(OH)CH), 4.60–4.10 (1H, br, CH(OH)CH), 3.38–3.33 (1H, dd, *J* 5.6 Hz, CH(OH)CH(COOH)). δ_{C} (CDCl₃) 177.0, 140.3, 130.9, 128.4, 128.0, 126.4, 121.3, 73.7, 57.7.

Acknowledgements

This work received financial support from the University of Newcastle. C.R. acknowledges the receipt of an EPSRC

quota studentship and travel award, and a MacRobertson Scholarship.

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