Synthesis of Benzyl Ketones through Indium-Mediated Solvent-Free Reaction of Acid Chlorides with Benzyltins under Ultrasound Irradiation

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Abstract

The reaction of acid chlorides with benzyltributyltin was successfully conducted in the presence of indium powder under solvent-free conditions. The corresponding benzyl ketone products were obtained in good to excellent isolated yields (60-85%). Under ultrasonic irradiation the reaction times are significantly reduced from 2-3 h to 10-20 min without affecting yields. Working with dibenzyldibutyltin as substrate it is possible the transference of two benzyl groups from tin, thus improving effective mass yield. Benzyltriphenyltin afforded the desired ketone although in moderate yield.

Keywords: Benzyltins, Benzyl ketones, Ultrasound, Solvent-free, Indium

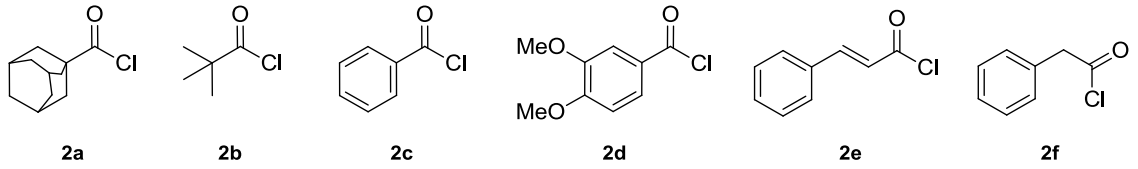
Introduction

Benzyl ketones are synthetically useful organic compounds which are found in natural products, dye precursors, materials and, in addition, exhibit interesting pharmacological and biological activities.[1] Currently, benzyl ketones have emerged as valuable intermediates for new functionalization strategies of unstrained C−C bonds.[2]

On the other hand, the development of indium-mediated synthetic methods has grown up in the recent literature due to the special properties of indium metal.[3] It is unaffected by air, moisture or oxygen at ambient temperature and, most importantly, the element itself is without any apparent toxicity. In this respect, we have established that this metal is a promoter of the mild, neutral and solvent-free reaction of acid chlorides with arylstannanes applied to the synthesis of hindered benzophenones[4] and alkyl aryl ketones under ultrasound irradiation.[5] Taking into account that, benzylstannanes are readily available and versatile precursors for the introduction of a variety of functional groups,[6] we now report an extension of our indium-mediated methodology directed towards the synthesis of benzyl ketones. A mechanism is proposed to explain the experimental results obtained.

Results and Discussion

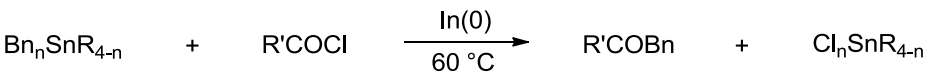
Initially, we examined the reaction between benzyltributyltin (**1**) and 1-adamantanecarbonyl chloride (**2a**, Figure 1) under the optimized reaction conditions we have previously established in the presence of indium metal (1 equiv) without ultrasonic irradiation.[5] After 2 h, the reaction was completed (monitored by TLC until disappearance of **1**) and the corresponding benzyl ketone **3a** was obtained in a good isolated yield (Table 1, entry 1). A control experiment showed that no reaction occurred in the absence of indium, indicating that the metal also acts as a promoter of this reaction (entry 2).



2a **2b** **2c** **2d** **2e** **2f**

Figure 1 Commercial acid chlorides employed

Table 1 Indium-mediated reactions of benzyltins with acid chlorides[a,b]



1, 4-6 **2** **3**

1 R=^{n}Bu, n=1; **4** R=Ph, n=1; **5** R=^{n}Bu, n=2; **6** R=^{n}Bu, n=3

Entry	Bn$_n$SnR$_{4-n}$	**2**	**3**	Without US		With US	
				Time (min)	Yield[c] (%)	Time (min)	Yield[c] (%)
1	**1**	**2a**	**3a**	120	85	10	82
2[d]	**1**	**2a**	**3a**	120	0	—	—
3	**1**	**2b**	**3b**	180	78	20	75
4	**1**	**2c**	**3c**	180	0	—	—
5	**1**	**2d**	**3d**	180	0	—	—
6	**1**	**2e**	**3e**	—	—	60	0
7[e]	**1**	**2f**	**3f**	—	—	10	60
8	**4**	**2a**	**3a**	90	55	15	52
9	**4**	**2b**	**3b**	—	—	10	45
10	**5**	**2a**	**3a**	—	—	10	68
11	**6**	**2a**	**3a**	—	—	15	14[f]

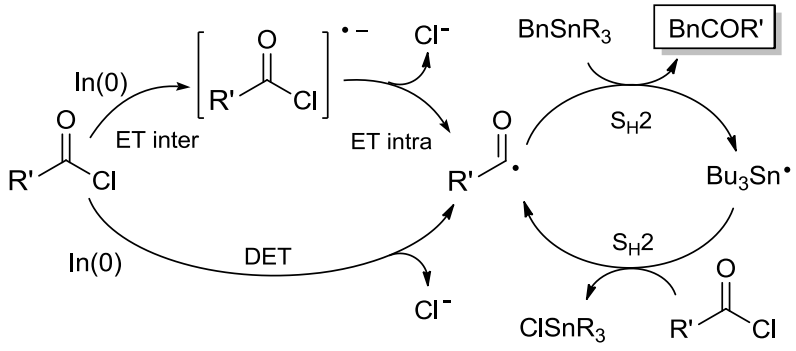
[a]All reactions were conducted in solventless conditions using 1.0 equiv of **1**, 1.2 equiv of **2** and 1.0 equiv of indium metal. [b]Oil bath (60°C). [c]Isolated yields (column chromatography) from 1.0 mmol scale experiment. [d]In absence of In(0). [e]Traces of $(BnCO)_2$ were detected (GC-MS). [f]Determined by GC quantization using tetradecane as internal standard.

On the other hand, while pivaloyl chloride (**2b**) reacted smoothly with **1** giving the benzyl ketone **3b** in 78 % yield (3 h, entry 3), the reactions of acid chlorides **2c** and **2d** were negative under analogous conditions, and **1** was almost completely recovered after 3 h (entries 4 and 5) in both cases.

Based on our previous experiences, we investigated the effect produced by ultrasonic irradiation on indium-mediated reactions of **2a** and **2b** with **1** under those optimized conditions.[5] Once again, the obtained results (entries 1 and 3) show that sonication noticeably reduced the reaction times (2-3 h to 10-20 min) without significantly affecting the yields. Unfortunately, no reaction took place with *trans*-cynnamoyl chloride (**2e**) although a moderate yield of ketone **3f** was obtained from phenylacetyl chloride (**2f**) under these reaction conditions.[7]

A promising result was obtained when the reaction of **2a** was conducted with benzylstannane **4** (entry 8) where the benzyl group was selectively transferred from tin - in preference to phenyl group- giving, either with or without ultrasound irradiation, acceptable yields of **3a**. A similar result gave the sonicated reaction of **2b** with **4** (entry 9). It should be noted that no evidence of competitive phenyl ketones were detected by GC-MS analysis. Among other aspects, these findings are so encouraging in regards to the low cost, lower toxicity and easier removal of the solid triphenyltin chloride.

Very recently, we have reported a theoretical interpretation with DFT methods of the limited experimental scope found with some aroyl chlorides in the solvent-free, indium-promoted reaction with arylstannanes.[8] Based on these findings, and taking into account that the known low bond dissociation energy of benzylic C-Sn bond facilitates homolytic reactions, a plausible mechanism for the reactions examined in the current work is outlined in Scheme 1.



Scheme 1 Proposed mechanistic pathways for the indium-mediated homolytic substitution of benzyltins with acid chlorides

Since the generation of equimolar amounts of non-benign organotin chlorides is a serious drawback from a sustainable standpoint, we also considered it interesting to study the possibility of transferring more than one benzyl group attached to tin. For this purpose, we applied the protocol to the reaction of **2a** with dibenzyldibutylstannane (**5**). After 10 min the starting stannane was consumed (TLC) and **3a** was obtained in a good isolated yield (68%, referred to the stoichiometric equation, entry 10). However, the same conditions applied to tribenzylbutylstannane (**6**), gave only 14% (GC) of **3a** together with large amounts of toluene as protodestannylation product (entry 11). Anyway, the employment of **5** implies the use of sub-stoichiometric amounts of organotin compounds and the formation of Bu_2SnCl_2 as by-product which is less toxic than Bu_3SnCl and easily converted into insoluble $(Bu_2SnO)_n$

Conclusions

In addition to the mild and neutral conditions, the method provides an attractive alternative to synthesize benzyl ketones due to the availability, air- and moisture-stability of benzylstannanes, as well as their compatibility with a variety of functional groups. Moreover, the selective transfer of benzyl group, from triphenyltin, or two benzyl groups, from the dibutyltin derivative, reduced the toxicity and the amount of non-benign organotin subproducts. Also, it is important to emphasize that no products of further benzylation of ketones was observed.

Further researches of the scope and mechanism of these reactions are currently in progress.

Experimental section

General experimental methods

All reactions were carried out under dry nitrogen. Acid chlorides were commercially available and fractionally distilled under nitrogen or recrystallized from hexane before use. Benzyltins **1,4-6** were synthesized from corresponding tin chlorides by Barbier-type sonicated reaction according to the literature procedures.[6] Reactions were monitored by thin-layer chromatography carried out on silica gel plates (60F-254) and visualized under UV light or using 5% phosphomolybdic acid in ethanol. External sonication was carried out using an ultrasonic probe (from Cole-Parmer 4710 series ultrasonic homogenizer of 20 kHz and 375 W) equipped with a 10 mm diameter titanium horn, which was immersed in an oil bath. Column chromatography was performed over silicagel 60 (70–230 mesh) doped with 10% of potassium fluoride.[9] The

NMR spectra were recorded on a 300 MHz spectrometer (300.1 MHz for ^{1}H, 75.5 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane, with residual non deuterated solvent resonance as internal reference ($CDCl_3$: δ 7.27 for ^{1}H and δ 77.0 for ^{13}C) and coupling constants (J) are in Hz. Identity and purity of the products (crude or purified) were established using a GC/MS instrument (HP5-MS capillary column, 30 m x 0.25 mm x 0.25 µm) equipped with 5977 A mass selective detector operating at 70 eV (EI). Program: 50 ºC for 2 min with increase 10 ºC/min to 280 ºC. For gas–liquid chromatography (GC) an instrument equipped with a flame-ionization detector and a HP5 capillary column (30 m x 0.25 mm x 0.25 µm) was used. Organotin chlorides by-products were recovered following the experimental procedure described in our previous work.[5]

Representative procedure for ultrasound assisted indium mediated reactions: Synthesis of 1-(1-adamantyl)-2-phenylethanone (3a)[10]

In a flame dried Schlenk tube (fitted with a Teflon plug valve) 1.2 mmol (0.240 g) of 1-adamantanecarbonyl chloride (**2a**) was added to a stirred mixture of 1.0 mmol (0.381 g) of benzyltributyltin (**1a**) and indium powder (0.148 g, 1.0 mmol) under a nitrogen gas stream. After purging the system with nitrogen by means of three pump-fill cycles, the tube was capped and immersed in an oil bath at 60 ºC. The ultrasonic titanium horn was placed into the bath to a distance of 10 mm to the wall and 5 mm from the bottom of the Schlenk tube and ultrasound was applied in a pulsed mode (duty cycle = 70 %; output power = 70 %) for 10 min. After addition of 10 % (m/v) solution of NaOH (2 mL) and 10 µL of tetradecane (internal standard), the mixture was stirred at room temperature for 15 min and then diluted with DCM (5 mL). Once the stirring was stopped for about 5 min, the supernatant liquid mixture was decanted into a separatory funnel. The organic phase was successively washed with water and brine, dried over Na_2SO_4, filtered, analyzed by GC, and then concentrated under vacuum. Purification by column chromatography on silica gel (60 Å, 70–230 mesh) doped with 10% of KF (hexanes/DCM 6:4) gave 0.208 g (82 %) of **3a** as a white solid; mp 34-35 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.51-6.91 (m, 5H), 3.69 (s, 2H), 1.99 (br, 3H), 1.79 (d, J = 2.9 Hz, 6H), 1.74-1.58 (m, 6H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) 210.90 (CO), 133.40 (C), 128.09 (CH), 125.83 (CH), 125.00 (CH), 45.38 (C), 41.26 (CH_2), 36.72 (CH_2), 35.03 (CH_2), 25.43 (CH); **MS** *m/z* (% rel. intensity, ion) 254 (2, $M^{+\cdot}$), 163 [45, ($M^{+\cdot}$-$Bn^{\cdot}$)], 135 [100, (1-Ad^{+})], 91 (56, Bn^{+}).

3,3-Dimethyl-1-phenyl-2-butanone (3b)[11]. Yield 0.132 g (75 %), colorless liquid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.26-7.07 (m, 5H), 3.72 (s, 2H), 1.12 (s, 9H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) 211.26 (CO), 133.42 (C), 128.01 (CH), 126.12 (CH), 125.07 (CH), 43.11 (C), 41.75 (CH_2), 24.89 (CH_3); **MS** *m/z* (% rel. intensity, ion) 176 (7, $M^{+\cdot}$), 91 (45, Bn^+), 85 [38, ($M^{+\cdot}$-$Bn^{\cdot}$)], 57 (100, $^tBu^+$).

1,3-Diphenylpropan-2-one (3f). Yield 0.126 g (60 %), light yellow solid; mp 32-36 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.28-7.16 (m, 3H), 7.09-7.05 (m, 2H), 3.65 (s, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) 204.13 (CO), 132.48 (C), 127.99 (CH), 127.21 (CH), 125.55 (CH), 47.59 (CH_2); **MS** *m/z* (% rel. intensity, ion) 210 (9, $M^{+\cdot}$), 119 [18, ($M^{+\cdot}$-$Bn^{\cdot}$)], 91 (100, Bn^+).

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§ Member of CIC

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