Ultrasonics Sonochemistry 20 (2013) 826–832

Contents lists available at SciVerse ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultson

Indium-mediated regioselective synthesis of ketones from arylstannanes under solvent-free ultrasound irradiation

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ARTICLE INFO

Article history:
Received 3 July 2012
Received in revised form 26 October 2012
Accepted 31 October 2012
Available online 22 November 2012

Keywords:
Ultrasound
Solvent-free
Aromatic ketones
Arylstannanes
Indium

ABSTRACT

The solvent-free indium-promoted reaction of alkanoyl chlorides with sterically and electronically diverse arylstannanes is a simple and direct method for the regioselective synthesis of primary, secondary and tertiary alkyl aryl ketones in good to excellent isolated yields (42–84%) under mild and neutral conditions. The protocol is also adequate for the synthesis of aryl vinyl ketones. Reaction times are drastically reduced (from 3–32 h to 10–70 min) under ultrasonic irradiation. Evidences for the involvement of a homolytic aromatic *ipso*-substitution mechanism, in which indium metal acts as radical initiator, are presented. It is possible the transference of two aryl groups from tin, thus improving effective mass yield, working with diarylstannanes as starting substrates.

1. Introduction

Ketones are vital building blocks in organic synthesis as well as an important functionality found in several natural products and pharmaceutical compounds. The Friedel–Crafts (F–C) acylation of aromatic compounds is the most common route for the synthesis of aromatic ketones [1]. Nevertheless, intrinsic limitations of F–C reactions are the substituent-directing effects, the reactivity substrate requirements and the fact that recovery and recycling of the catalyst is seldom possible after aqueous work-up and a large amount of toxic waste is generated. On the other hand, Pd-catalyzed cross-coupling reactions of acyl halides with organometallic reagents provide a direct procedure for the synthesis of isomeric ketones [2]; a drawback is that Pd-catalysts are expensive and that it is usually necessary to find the appropriate catalytic protocol for each pair of reactants. We have been involved in the synthesis of arylstannanes as well as in their application as intermediates in organic synthesis [3]; recently, based on the exceptional leaving group ability of the trialkylstannyl group in electrophilic aromatic substitutions we have developed new straightforward procedures for the regiospecific [4] mono-, bi- and triaroylation of aromatic rings by the reaction of mono-, bi- and tristannylarenes with different aroyl chlorides [5]. Moreover, we have proposed an efficient catalyst-free route (*o*-dichlorobenzene, 180 °C) for the selective synthesis of tertiary alkyl aryl ketones in good to high yields, without the generation of alkylbenzenes as by-products, by the reaction of arylstannanes with tertiary aliphatic acyl chlorides [6]. Unfortunately, under a similar protocol acyl chlorides bearing α-hydrogens lead only to protodestannylated products due to the presence of HCl generated under the reaction conditions, probably, by a β-elimination of the alkanoyl chloride [6]. In recent years, the development of indium-mediated synthetic methods has grown up in the literature due to the special properties of indium metal [7]. Thus, 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 indium metal is a promoter of the solvent-free reaction of aroyl chlorides with arylstannanes applied to the synthesis of hindered benzophenones [5c]. Based on this experience we considered interesting to explore the application of a similar protocol for the synthesis of alkyl aryl ketones, specially taking into account the above mentioned limitation found in our catalyst-free route [6].

In the last decades, ultrasound irradiation has emerged as an eco-environmental technology in green chemistry [8]. It has been increasingly used as an alternative energy source to promote several organic transformations in higher yields, shorter reaction times and milder conditions, being considered a clean and useful protocol compared with traditional methods [9]. A literature survey demonstrates that many synthetic protocols using metals or organometallic reagents could be promoted by ultrasonic irradiation [10]. Thus, it has beneficial effects on indium-mediated reactions [10,11], and the existence of SET pathways may be

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http://dx.doi.org/10.1016/j.ultsonch.2012.10.018

probable in these type of reactions [7]. Additionally, many solvent-free protocols can be conducted smoothly by sonication [12].

On the base of these antecedents we considered really interesting to study the effect produced by ultrasonic irradiation on our protocol.

Thus, we report herein the synthetic potential of the ultrasound irradiated, solvent-free, indium-promoted reaction of acid chlorides with arylstannanes; we have checked the reusability of the indium metal and a special work-up was carried out to recover the organotin by-products. The study resulted in an attractive process for the synthesis of alkyl aryl ketones under mild and neutral conditions.

2. Results and discussion

We started our study by synthesizing a series of sterically and electronically diverse arylstannanes (**1a–h**) which were then subjected to the reaction with different acid chlorides (**2a–g**) under the conditions we have previously established, that is, solvent-free, in the presence of indium powder [5c].

An analysis of the results summarized in Table 1 shows that electronic effects have a notable influence in the reaction; thus, arylstannanes bearing electron-releasing groups gave the corresponding ketones even at room temperature meanwhile the presence of electron-withdrawing groups made it necessary to work at higher temperatures (for example, compare entry 2 with 3 and 4). Moreover, the reaction of **2a** with **1h**, bearing a *p*-cyano substituent, was negative even after 72 h at 80 °C and the starting substrate was almost recovered (entry 7). On the other hand, the substitution pattern of the aromatic ring did not greatly affect the reaction and *ortho*-, *para*- and *meta*-substitution were well tolerated. In general, the reactions gave, as a single product, the corresponding ketones resulting from the strict *ipso*-substitution of the stannyl group, allowing the synthesis of ketones with high specificity. Thus, even the more sterically hindered 2,6-dimethylphenylstannane (**1g**) was also successfully *ipso*-acyldestannylated giving the corresponding ketones **3ga**, **3gb**, **3gf** and **3gg** in good isolated yields (47–75%). It should be mentioned that in experiments 6, 14 and 22 traces of an isomeric ketone were detected (GC), generated by direct acylation of the aromatic ring followed by protodestannylation. On the other hand, the negative reaction between **1g** and **2c** is probably due to steric effects (entry 19). Unfortunately, it was not possible to overcome the strong *para*-directing effect of the OMe group producing, whatever the acyl chloride employed, high amounts of the ketone generated by direct acylation of the ring (entries 1 and 18), being these results consistent with those obtained previously in the aroylation of arylstannanes [5c].

A global evaluation of the results indicates that the method can be used to produce ketones either from primary, secondary or tertiary alkanoyl chlorides.[2] By the way, due to its low boiling point, the reactions with acetyl chloride must be carried out in solution being benzotrifluoride chosen as solvent in view of its properties (entry 23) [13]. Furthermore, experiment 22 shows that by using cinnamoyl chloride (**2g**) afforded the desired ketone although in moderate yield (47%). On the other hand, electron withdrawing groups on the acyl chloride moiety showed a negative effect. Thus, while the reaction of pivaloyl chloride (**2d**) with **1b** produced the desired ketone in 55% yield (22 h, 60 °C), under analogous conditions the reaction of the similar acyl chloride **2e** with **1b** was negative and the starting substrate was almost recovered after 24 h of reaction (entries 20 and 21).

It should be mentioned that each reaction was, in principle, performed at the lowest temperature which allowed keeping the stirring of the reaction mixture during reaction time. Nevertheless, it is important to note that an increase in reaction temperature causes a sharp reduction of reaction times (entries 3 vs. 4; 8 vs. 9).

We carried out control experiments which showed that no reaction occurred in the absence of indium, indicating that the metal acts as a promoter of these reactions. On the other hand, the addition of galvinoxyl radical (0.5 equiv) to a couple of reactions produced a marked retardation effect and they did not proceed efficiently comparing with blank ones. Based on these results, we believe that these reactions proceed initially through a single-electron transfer (SET) from indium to the acyl chloride with generation of an acyl radical,[3] which reacts with the arylstannane through a homolytic *ipso* aromatic substitution affording the ketone. The selective *ipso*-substitution is a consequence of the enhanced hyperconjugation of the unpaired electron with the β-carbon-tin bond (β-effect) [14]. The tin radical should be rapidly lost and reacts with the alkanoyl chloride, regenerating the acyl radical (Scheme 1). It should be mentioned that the reaction also takes place using sub-stoichiometric amounts (0.2 equiv) of In(0) although the yield decrease from 84% to 71% (entries 9 and 10).

Next, since sonication is able to affect heterogeneous systems which include radical mechanisms [9], we studied the effect produced by ultrasonic irradiation over these reactions.

The optimal conditions for carrying out the irradiated reactions were found by the reaction of tributylstannyl-3-chlorobenzene (**1f**) and butanoyl chloride (**2a**) in the presence of indium (Table 2). The model reaction was carried out using an ultrasonic probe (from Cole-Parmer ultrasonic homogenizer-4710 of 20 kHz and 375 W) equipped with a 10 mm diameter titanium horn. Experiments were conducted in closed glass reactors along with the horn immersed in a bath. The first experiments were performed in a water/detergent bath [15] (60 °C initial temperature) working at 70% and 90% of output power and in a pulsed mode with different duty cycles (70% or 80%). The results indicated that the reaction proceeded similarly under the diverse conditions employed so, in the following, 70% of power out and 70% duty cycles were used. Moreover, as cavitation is dependent on temperature [16], one experiment was performed at 100 °C (initial temperature, oil bath); under these conditions product **3fa** was obtained in a similar yield but in really shorter reaction time (3 min). Probably, the increase in the reaction rate at 100 °C is due to the decrease of the reaction mixture viscosity (solvent-free) which improves the molecular diffusion [12a]. These results enable us to affirm that in comparison with the conventional method (Table 1, entry 5) the major advantage of ultrasound application is the significant decrease in the reaction time (from 5 h at 80 °C under classical conditions to 10 min at 60 °C or 3 min at 100 °C, under irradiation).

The optimized conditions were applied to a representative series of reactions, shown in Table 3, in order to compare with those reactions carried out by the conventional method (Table 1). It should be mentioned that the reactions were performed at the lowest temperature which kept a homogeneous mixture of substrate and reactant.

The results obtained show that, in all cases, sonication dramatically reduced the reaction times without significantly affecting the yields. Once more, ultrasound enhanced the rate of a reaction and, consequently, reduced energy consumption. Comparing experiments 4 and 5, the reaction took place even using sub-stoichiometric amounts of indium but giving lower yields of ketone (62% vs. 47%). On the other hand, experiments 7 and 9 show that it was possible to performed reactions, in a reasonable reaction time, without

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[2] It was found that 2.0 equiv. of tertiary acyl chloride is required in order to shorten reaction times.

[3] Indium metal is capable of promoting SET processes. See Ref. [7].