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Note

Catalyst-free alkanoylation of aromatic rings *via* arylstannanes. Scope and limitations

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ABSTRACT

The reaction of alkanoyl chlorides with arylstannanes in 1,2-dichlorobenzene (180 °C) is a simple and direct route for the catalyst-free and regioselective synthesis of tertiary alkyl aryl ketones in good to excellent isolated yields (55–77%). Nevertheless, under similar conditions, reactions carried out with alkanoyl chlorides bearing α-hydrogens render only the product of protodestannylation.

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1. Introduction

Ketones are vital building blocks in organic synthesis as well as an important functionality found in several natural products and in various pharmaceutical compounds. Electrophilic aromatic substitution (EAS) such as Friedel–Crafts (F–C) acylation [1] and cross-coupling reactions of acyl chlorides with organometallic reagents [2] are presumed to be the preferences for the synthesis of aromatic ketones. Although these reactions are efficient methods to form ketones in good yields, there are some disadvantages related with them. Thus, 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, although Pd-cross-coupling reactions are effective, Pd-catalysts are expensive and it is usually necessary to find the appropriate catalytic protocol for each pair of reactants. Recently, based on the exceptional leaving group ability of the trialkylstannyl group in electrophilic aromatic substitutions, we have proposed efficient catalyst-free straightforward routes for the mono-, bi- and triaroylation of aromatic rings, by the reaction of mono-, bi- and tristannylarenes with different aroyl chlorides [3].

The results obtained encouraged us to explore its application to the mono-, bi- and trialkanoylation of aromatic rings. Now, we report the synthetic scope and limitations of these reactions as well as the special work-up carried out in order to recover the Bu_3SnCl generated.

2. Results and discussion

As electrophilic attack is accelerated by the presence of electron-donating groups on the arene system we started the study of the reactivity of tributyl(4-methoxyphenyl)stannane (**1**) towards different commercially available alkanoyl chlorides such as acetyl and butyryl chloride under the best reaction conditions previously established for the synthesis of triaryl ketones, that is, in 1,2-dichlorobenzene as solvent, at 180 °C [3b]. Unfortunately, the desired ketones were not detected, no starting material was recovered and the reactions led only to the corresponding protodestannylated product, i.e., anisole, indicative of the presence of important amounts of HCl in the reaction mixture. Taking into account that we reduce to an extreme the presence of HCl in the starting acylation agents, we considered that the HCl should be generated under the reaction conditions, probably, by a β-elimination of the alkanoyl chloride [4]. In order to minimize this undesirable reaction we decided to work at lower temperature (130 °C, [3a]). After longer reaction times (72 h) an important decrement of the amount of protodestannylated product was observed but, unfortunately, large amounts of starting substrate **1** was recovered (ca. 80%) and only traces of the desired ketone were detected (GC/MS). In order to prove our hypothesis, we decided to study the reaction of **1** with 1-adamantylcarbonyl chloride (**13a**) which does not possess an α-hydrogen. With pleasure we observed that, after 1 h, the desired ketone, i.e., 1-adamantyl-4-methoxyphenylmethanone (**14a**) was obtained in 76% yield (entry 1, Table 1).

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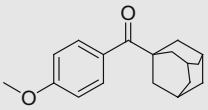
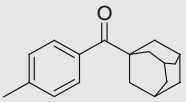
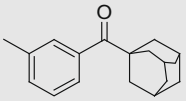
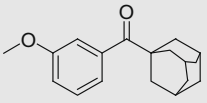
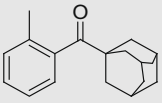
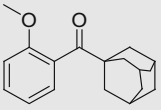
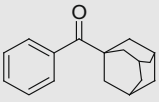
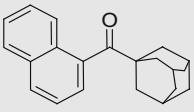
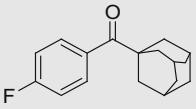
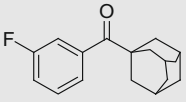
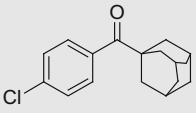
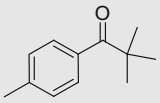
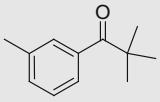
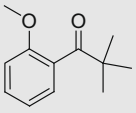
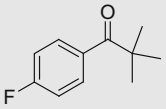
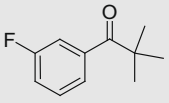
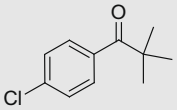
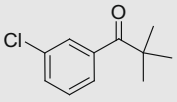
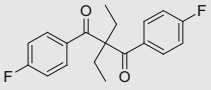
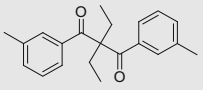
Table 1
Reactions of arylstannanes with acyl chlorides in 1,2-dichlorobenzene.[a]

Entry	Stannane	RCOCl[b]	Ketone	Time (h)	Yield (%)[c]
1	1	**13a**	 **14a**	1	76(68)
2	**2**	**13a**	 **15a**	3	75(66)
3	**3**	**13a**	 **16a**	4	73(67)
4	**4**	**13a**	 **17a**	3	60(58)
5	**5**	**13a**	 **18a**	24	72(66)
6	**6**	**13a**	 **19a**	16	62(55)
7	**7**	**13a**	 **20a**	5	74(69)
8	**8**	**13a**	 **21a**	4	36(30)
9	**9**	**13a**	 **22a**	2	72(68)
10	**10**	**13a**	 **23a**	1.5	84(77)
11	**11**	**13a**	 **24a**	6	80(70)
12	**2**	**13b**	 **15b**	4	80(73)
13	**3**	**13b**	 **16b**	5	70(62)
14	**6**	**13b**	 **19b**	16	69(60)
15	**9**	**13b**	 **22b**	3	81(70)
16	**10**	**13b**	 **23b**	2	82(71)
17	**11**	**13b**	 **24b**	7	79(68)
18	**12**	**13b**	 **25b**	6	75(66)
19[d]	**11**	**13c**	 **22c**	48	0
20[d]	**3**	**13c**	 **16c**	48	0

[a] All reactions were performed at 180 °C (oil bath).
[b] RCOCl (1.2 equiv) were used unless otherwise stated.
[c] Determined by GC.; isolated products between parentheses as an average of at least two independent runs.
[d] RCOCl (2.4 equiv).

In view of this result we synthesized a series of electronically diverse starting tributylarylstannanes **1**–**12** (Fig. 1,) by reaction of the corresponding aryl Grignard reagent with tributyltin chloride [5], and we studied their reactivity towards commercially available tertiary alkanoyl chlorides **13a–c** (Fig. 1).

The results obtained are summarized in Table 1.

It can be seen that the reactions of arylstannanes bearing either electron-withdrawing or electron-releasing groups proceed in good to high yields with both **13a** and **13b**. As it was predictable,

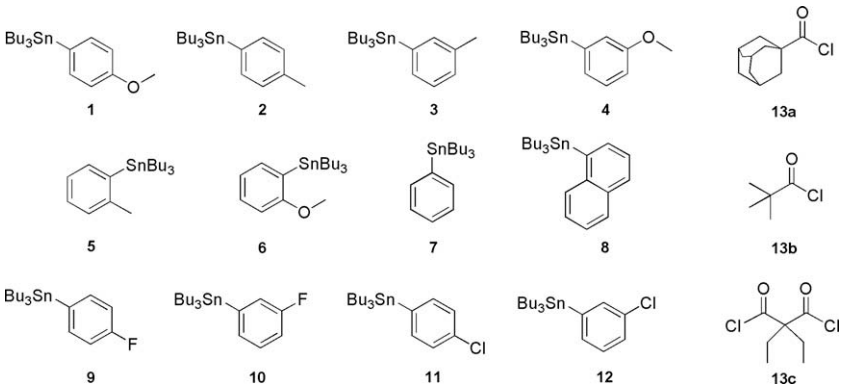


Fig. 1. Starting tributylarylstannanes and acid chlorides.

those arylstannanes carrying activating groups in *meta*- and *para*-position (**1**–**4**) (entries 1–4, 12 and 13) react faster than those carrying a deactivating group such as chlorine in the same positions (**11** and **12**) (entries 11, 17 and 18). The decreased reactivity shown by substrates **5** and **6** (entries 5, 6 and 14) are, probably, due to steric effects. Nevertheless, the results demonstrate that the route proposed is effective for the synthesis of more crowded ketones. On the other hand, the increased reactivity shown by substrates **9** and **10** (entries 9, 10, 15 and 16), which support a fluorine group, is in agreement with the "anomalous" reactivity of fluorobenzene in EAS [6]. Moreover, our results demonstrate that in these reactions substrates **9** and **10** react faster even than substrates bearing activating substituents such as **2**, **3** and **4**.

Also, a global evaluation of the results obtained indicates that **13b** is less reactive than **13a**, rendering similar yields but after longer reaction times (compare entries 2/12, 3/13, 9/15, 10/16 and 11/17).

A series of competitive experiments were carried out to confirm the relative reactivity observed in the previous reactions. For example, a mixture of **9** and **10** in a 1:1 equivalent ratio was allowed to react with 1 equivalent of **13a** for 2 h and the products were analyzed by GC/MS. The reaction led to a mixture of the respective ketones, **22a** and **23a**, in 1:1.5 ratio (Eq. (1)). A similar result was obtained when a mixture of **9** and **10** react with **13b** (1:1:1), rendering ketones **22b** and **23b** in 1:1.4 ratio (Eq. (2)). These results confirm the observed higher reactivity of substrate **10** over substrate **9** towards these acylation reagents (compare entries 9/10 and 15/16).

$$\underset{(1\ \text{equiv})}{9} + \underset{(1\ \text{equiv})}{10} + \underset{(1\ \text{equiv})}{13a} \rightarrow \underset{(1:1.5)}{22a + 23a} \quad (1)$$

$$\underset{(1\ \text{equiv})}{9} + \underset{(1\ \text{equiv})}{10} + \underset{(1\ \text{equiv})}{13b} \rightarrow \underset{(1:1.4)}{22b + 23b} \quad (2)$$

On the other hand, we carried out another competitive reaction of **3** and **10** (1:1) towards **13b** (Eq. (3)). The result obtained (**16b**:**23b**, 1:1.3) corroborate the higher reactivity of substrates containing fluorine over substrates carrying common activating groups.

$$\underset{(1\ \text{equiv})}{3} + \underset{(1\ \text{equiv})}{10} + \underset{(1\ \text{equiv})}{13b} \rightarrow \underset{(1:1.3)}{16b + 23b} \quad (3)$$

Finally, the higher reactivity of stannylarenes towards **13a** over **13b** was corroborated by the competitive reactions resumed in Eqs. (4) and (5).

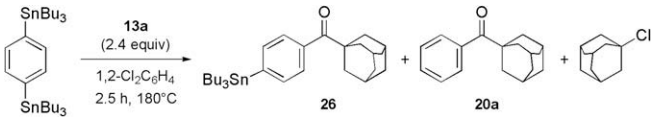
$$\underset{(1\ \text{equiv})}{13a} + \underset{(1\ \text{equiv})}{13b} + \underset{(1\ \text{equiv})}{3} \rightarrow \underset{(2.3:1)}{16a + 16b} \quad (4)$$

$$\underset{(1\ \text{equiv})}{13a} + \underset{(1\ \text{equiv})}{13b} + \underset{(1\ \text{equiv})}{11} \rightarrow \underset{(2:1)}{24a + 24b} \quad (5)$$

It should be mentioned that in all the experiments carried out, small amounts (not quantified) of *ipso*-protodestannylation products were detected (CG/MS), which probably result from minor HCl impurities in the acyl chloride. These protodestannylation products are irrelevant compared with the yields of the corresponding ketones obtained.

In view of our results we considered that the commercially available acyl chloride **13c** could be a good reagent for an efficient acylation reaction in which two bonds could be formed in one step, leading to the corresponding β-diketone. So, we carried out the reaction of both substrates **9** and **3** with **13c** (ratio 2.4/1). Unfortunately, even after 48 h at 180 °C the corresponding β-diketones were not detected and high amounts of starting substrates were recovered (GC/MS) (entries 19 and 20).

With the results obtained in hand and based on our previous experience [3b], with the main goal of introducing more than one alkanoyl group in an aromatic ring, we decided to study the reactivity of bistannylarenes towards **13a**. First, we carried out the reaction of 1,4-bis(trimethylstannyl)benzene with **13a** (1/2.4, 2.5 h, 180 °C) and the crude product was analyzed by GC/MS. The reaction led to a mixture of the monoalkanoyldestannylation product, i.e., 1-adamantyl-4-trimethylstannylphenylmethanone (**26**) and 1-adamantyl-phenylmethanone (**20a**) in an 8.5/1 ratio, accompanied by starting arylstannane and chloroadamantane. The desired bisalkanoylation product was not detected (Eq. (6)).



(6)

An increment in the reaction time (5 h) led to a qualitatively analogous product distribution. Nevertheless, we observed that meanwhile the yield of compound **26** decreased with time, the yield of compound **20a** increased (**26**/**20a**, 1.8/1). It should be mentioned that it was also detected larger amounts of chloroadamantane and only traces of starting arylstannane. The results obtained showed that it was not possible to introduce a second alkanoyl group under these reaction conditions. Taking into account that the monoacylated product **26** should be an excellent intermediate for an asymmetric bifunctionalization of the ring [7], we carried out a third reaction using a defect of **13a** (substrate/**13a**, 1/1.2, 5 h) in order to increase the yield of **26**. The GC/MS showed that **26** was the main product and only traces of **20a** were detected, but, unfortunately, large amounts of starting arene were also present which made impossible the isolation of **26** from this mixture. It should be mentioned that, under these conditions, chloroadamantane was not present among the reaction products.

Furthermore, the reaction of 1,3-bis(trimethylstannyl)benzene with **13a** (1/2.4, 2.5 h) led to a mixture of **20a** and chloroadamantane; no monoalkanoyldestannylation product, i.e., 1-adamantyl-3-trimethylstannylphenylmethanone (**27**), was detected. When we used a defect of **13a** (substrate/**13a**, 1/1.2, 2.5 h) compound **27** was obtained together with **20a** in a 1/1.8 ratio and chloroadamantane was not present. No starting substrate was detected under both reaction conditions. We were not able to isolate compound **27** from the mixture obtained.

The results indicate that when there is an excess of **13a** in the reaction media (substrate/**13a**, 1/2.4), compound **20a** increased in time at expense of compounds **26** or **27**. Moreover, the substantial amount of chloroadamantane found under these conditions could be explained as a result of decarbonylation of the unreactive excess of **13a**[2]. It should be mentioned that no alkylation products were detected in agreement with results reported by Neumann [8].

3. Conclusions

The present results show that the protocol presents some limitations in the alkanoylation of an aromatic ring. Thus, acyl chlorides bearing α-hydrogens lead only to protodestannylated products, and it is not possible to introduce a second alkanoyl group, in contrast to the bisaroylation reactions [3b]. Nevertheless, the reaction provides a new simple and direct route for the selective synthesis of tertiary alkyl aryl ketones in good to high yields. Due to the high *ipso*-directing force of the tributylstannyl group [9], all the reactions studied were regioselective and they went, exclusively, through an *ipso*-acyldestannylation independently whether the directing influences of the aryl substituents and the tributylstannyl group are either matched (compounds **1**, **2**, **5**, **9** and **11**) or mismatched (compounds **3**, **4**, **10** and **12**), taking place even with substrates bearing deactivating groups. Thus, this approach overcomes the limited substrate scope and reduced regiocontrol of traditional Friedel–Crafts acylation methods.

It should be mentioned that, in the last years, different strategies have been developed which could be applied to the synthesis of these bulky ketones, for example, F–C reactions catalyzed by In [10], $BiCl_3$ [11] or silica [12]; cross-coupling reactions with organoboron reagents [13]; the reaction of acyl chlorides and Grignard reagents catalyzed by metal halides [14] and the Pd-mediated cross-coupling of α-oxocarboxylic acids and aryl bromides [15]. The method here proposed enables the high regioselective formation of bulky ketones without employing a catalyst, that is, a more eco-friendly acylation of aromatic rings.

However, one disadvantage is the generation of tributyltin chloride as secondary product. Because of the environmental problems caused by the well-known toxicity of triorganotin residues, we considered really important to trap the Bu_3SnCl generated. With this aim, product purification was carried out by chromatography on a silica gel column doped with KF [16]. Thus, organotin residues were totally removed from final products, trapped as Bu_3SnF. Finally, based on results reported by Mitchell [17], Bu_3SnCl was recuperated (c.a. 80%) by treating the silica gel with an excess of NaCl in THF (see Section 4).

In order to decrease the level of pollution, we have started the study of an alternative route to obtain aryl ketones using polymer-supported organotin reagents as key intermediates. This strategy should combine the advantages of the method described in this paper with those expected from polymer-supported tin reagents. This work is in progress.

[2] Chloroadamantane was detected (CG/MS) after heating (180 °C, 5 h) a solution of **13a** in 1,2-dichlorobenzene.

4. Experimental

Aryltins were prepared according to literature methods [5].

4.1. Representative procedure for alkanoyldestannylation. Preparation of 1-adamantyl-4-methoxyphenylmethanone (*14a*; Table 1, entry 1)

In an oven-dried 25 mL heavy walled Schlenk tube fitted with a teflon plug valve, 0.240 g (1.2 mmol) of 1-adamantylcarbonylchloride (**13a**) were added to a stirred solution of tributyl(4-methoxyphenyl)stannane (**1**, 0.398 g, 1.0 mmol) in 1,2-dichlorobenzene (1 mL) under a nitrogen atmosphere. The system was purged with nitrogen by means of three vac-refill cycles and the reaction mixture was heated at 180 °C (oil bath) for 1 h (monitoring the disappearance of **1** by TLC). After addition of 10% (m/v) solution of NaOH (2 mL), the mixture was stirred at room temperature for 15 min and then diluted with ether (5 mL). The organic phase was successively washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel doped with 10% of KF[16] (hexane/CH_2Cl_2 = 60:40) gave **14a** as a white solid (0.184 g, 68%); mp = 64–66 °C; *Rf* = 0.33 (hexane/EtOAc = 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 8.9 Hz), 6.88 (d, 2H, J = 8.8 Hz), 3.82 (s, 3H), 2.05 (br, 9H), 1.76 (br, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.8 (CO), 161.4 (C), 131.0 (C), 130.0 (CH), 113.0 (CH), 55.1 (CH_3), 46.6 (C), 39.3 (CH_2), 36.5 (CH_2), 28.6 (CH); EIMS *m/z* (rel intensity) 270 (M^+, 10), 135 (100), 107 (12). Anal. Calcd for $C_{18}H_{22}O_2$ (270.37): C, 79.96; H, 8.20. Found: C, 81.16; H, 8.43%.

4.2. Recovering method for tributyltin chloride

After flash chromatographic procedure (10.0 g of 40–63 μm silica gel for 1.00-mmol scale reaction) the column was eluted with 100 mL of THF. The silica was dried using compressed air and poured into a 100-mL round-bottomed flask fitted with a condenser and a nitrogen T-joint. Sodium chloride (293 mg, 5.00 mmol) and 50 mL of dry THF were added and the mixture was heated at reflux with stirring for 4 days. It is then allowed to cool and poured into a chromatography column plugged with a small piece of cotton wool. All of the THF was drained with air pressure and then the column was eluted with ether (2 × 50 mL). The combined ethers were concentrated in vacuo giving tributyltin chloride in ca. 80% with respect to the starting aryltributylstannane.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2009.07.019.

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