

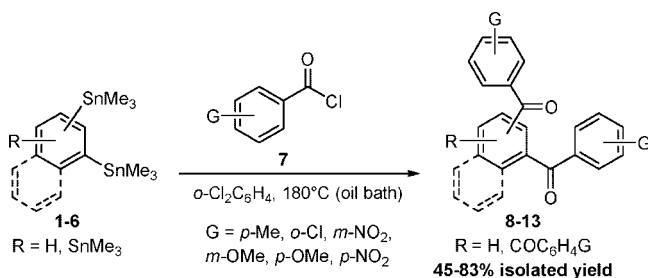
Efficient Catalyst-Free Bi- And Triarylation of Aromatic Rings in a Single Step

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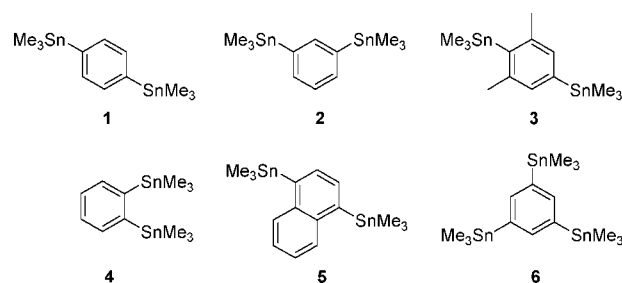


The exceptional leaving group ability of the trimethylstannyl group in electrophilic aromatic substitutions makes possible the synthesis, in a single step, of bi- and triarylarenes through the catalyst-free, regioselective reaction of bi- and tristannylarenes with different aryl halides in *o*-dichlorobenzene as solvent. Specific di- and triketones are obtained in good to excellent yields (45–83%).

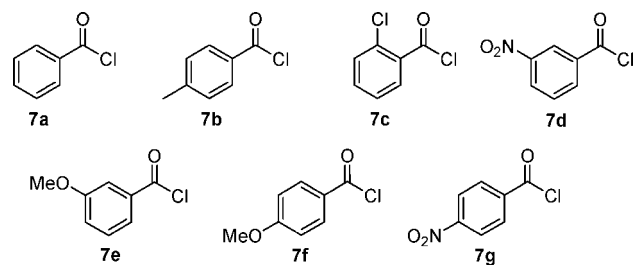
Ketones are vital building blocks in organic synthesis as well as an important functionality found in several natural products and in various pharmaceutical compounds. Electrophilic aromatic substitution such as Friedel–Crafts (F–C) acylation¹ and cross-coupling reactions of acyl chlorides with organometallic reagents² are presumed to be the preferences for the synthesis of wholly aromatic ketones.

In the field of organic synthesis, one important way to achieve efficiency in a reaction is to perform more than one reaction type in a single pot. Usually, diacyl halides are the preferred starting materials for the synthesis of diarylbenzenes involving either a F–C reaction with the appropriate aryl derivative³ or a transition metal-catalyzed cross-coupling reaction with organometallic compounds.⁴ In contrast, there are only few antecedents associated with an electronically counter process, i.e., the reaction of phenylendimetal compounds with acyl halides

allowing the simultaneous introduction of more than one acyl group in an aromatic ring. These antecedents are connected with the palladium-catalyzed cross-coupling reaction of phenylene-dizincs with acyl chlorides⁵ and with the palladium-catalyzed carbonylative cross-coupling reaction of triorganoindiums with di- and tri-iodobenzenes.⁶ Recently, based on the exceptional leaving group ability of the trimethylstannyl group in electrophilic aromatic substitutions, we have informed the synthesis of unsymmetrical diarylketones by the reaction of aroyl chlorides with arylstannanes, avoiding the use of catalysts.⁷ The results obtained encouraged us to explore its application to efficient reactions in which more than one bond is formed in one step. In this paper we are pleased to inform that bi- and tristannylarenes are useful partners to synthesized bi- and triarylarenes in a simple step by their catalyst-free reaction with different aroyl halides. As far as we know these are the first examples involving organostannanes.



We prepared a series of starting materials supporting two or three trimethylstannyl moieties attached to the aromatic ring (**1–6**)⁸ and we studied their reaction toward different commercially available aroyl chlorides under the reaction conditions previously established for the synthesis of diarylketones, that is, in chlorobenzene as solvent, at 130 °C.⁷ The results obtained are summarized in Table 1.



At first, we carried out the reaction of 1,4-bis(trimethylstannyl)benzene (**1**) with benzoyl chloride (**7a**) (**1/7a**, 1/2.4), and we were pleased to observed that, after 42 h, the desired

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TABLE 1. Reactions of Arylstannanes with Aroyl Chlorides in Chlorobenzene^a

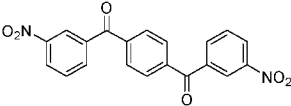
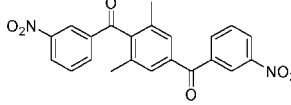
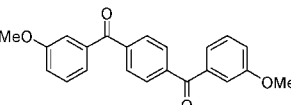
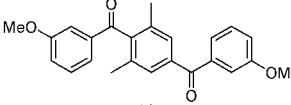
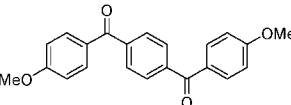
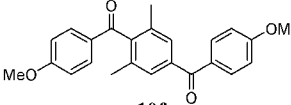
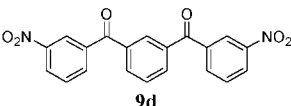
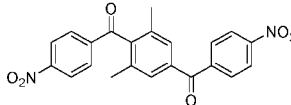
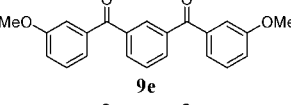
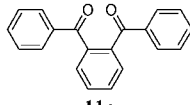
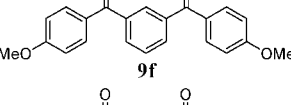
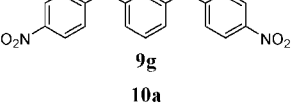
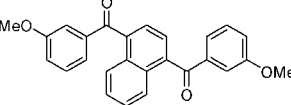
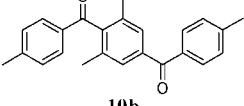
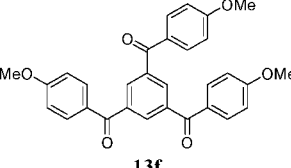
entry	stannane	ArCOCl	ketone	time (h)	yield (%) ^b
1	1	7a		42	56
2 ^c	1	7a	8a	26	82
3	2	7a		40	62
4 ^c	2	7a	9a	24	88
5	1	7b		48	42
6 ^c	1	7b	8b	26	73
7	2	7b		56	68
8 ^c	2	7b	9b	26	85
9	2	7c		112	37
10 ^c	2	7c	9c	74	48
11	1	7c		118	32
12 ^c	1	7c	8c	72	61
13	3	7a		23	72
14	3	7c		48	47
15	5	7a		48	50
16 ^d	6	7a		74	25

^a ArCOCl (2.4 equiv) was used unless otherwise stated. ^b Determined by GC. ^c ArCOCl (4 equiv). ^d ArCOCl (3.6 equiv).

diketone, i.e., 1,4-phenylenebis(phenylmethanone) (**8a**) was obtained in 56% yield (entry 1). A similar reaction carried out with arylstannane **2** proceeded efficiently giving 1,3-phenylenebis(phenylmethanone) (**9a**) (62%, 40 h) (entry 3). The results obtained in the reactions of **1** or **2** with either 4-methylbenzoyl chloride (**7b**) or 2-chlorobenzoyl chloride (**7c**) under similar conditions demonstrate that the reactions also proceed with acid chlorides bearing electron-donating or electron-withdrawing groups (entries 5, 7, 9, and 11). Moreover, the reactions of arylstannanes **3** and **5** with acid chlorides **7a** and **7c** also rendered the desired diketones, i.e., (2,6-dimethyl-1,4-phenylene)bis(phenylmethanone) (**10a**, 72%, 23 h) (entry 13), (2,6-dimethyl-1,4-phenylene)bis[2-chlorophenylmethanone] (**10c**, 47%, 48 h) (entry 14), and naphthalene-1,4-diylbis(phenylmethanone) (**12a**, 50%, 48 h) (entry 15), respectively. It should be mentioned that, in all the experiments, the desired triaryldiketones were accompanied with 15–20% of the corresponding diarylketones, probably as a result of the protodestannylation of one stannyl group under the reaction conditions. Moreover, in the reactions carried out with compound **3** (entries 13 and 14) there were detected (CG/MS) both isomeric monoketones in comparable yields, indicating that there is not a remarkable preference for the electrophilic attack on carbon-1 instead of carbon-4 as it was expected due to the existence of neighboring groups on the arene system.⁷ We also studied the reaction of 1,3,5-tris(trimethylstannyl)benzene (**6**) with benzoyl chloride in order to determine the scope of this reaction for the simultaneous triaroylation of the aromatic ring. With satisfaction we found that the reaction led to benzene-1,3,5-triyltris(phenylmethanone) (**13a**) even though in a low yield (25%) accompanied with a large amount of **9a** (65%).

With these results in hand and with the main goal of reducing reaction times and byproducts, we decided to study the influence of an increment of the ratio aroyl chloride/substrate from 2.4/1 to 4/1. The results obtained demonstrated the effectiveness of this change. In all the experiments carried out, reaction times and monoketone yields were decreased meanwhile yields of diketones were increased (entries 2, 4, 6, 8, 10, and 12). However, this method requires an important excess of acid chlorides which were destroyed during the usual aqueous workup leading to large amounts of waste. Looking for alternative reaction conditions in order to minimize the waste problem, we decided to carry out the reactions at higher temperatures (180 °C) using 1,2-dichlorobenzene as solvent. To demonstrate the efficiency and scope of the method, we applied this system to a variety of organostannanes and of aroyl chlorides. The results summarized in Table 2 demonstrate the efficiency of these reaction conditions. Thus, reaction times decreased dramatically at elevated temperatures without affecting the yield: compare experiments 1, 2, 3, 7, 8, 9, 14, 16, and 22 in Table 2 with the analogous experiments resumed in Table 1. Moreover, the undesired monoketones were detected only in tiny amounts, irrelevant compared with the yields of the diketones obtained, improving their isolated yields. The results obtained in experiment 21 demonstrate that it is also possible to insert two aroyl groups in adjacent positions of the aromatic ring with high yields. Furthermore, experiments 24 and 25 enable us to say that this method could be also applied to the triaroylation of the aromatic ring in a simple step. Other methods available for the synthesis of such

TABLE 2. Reactions of Arylstannanes with Aroyl chlorides in 1,2-Dichlorobenzene^a

entry	stannane	ArCOCl	ketone	time (h)	yield (%) ^b	entry	stannane	ArCOCl	ketone	time (h)	yield (%) ^b
1	1	7a	8a	5	79(70)	16	3	7c	10c	6	57(49)
2	1	7b	8b	7	76(68)						
3	1	7c	8c	36	65 (51)						
4	1	7d	 8d	7	(45)	17	3	7d	 10d	7	(59)
5	1	7e	 8e	6	62(53)	18	3	7e	 10e	8	74(61)
6	1	7f	 8f	6	85(77)	19	3	7f	 10f	7	92(83)
7	2	7a	9a	4	93(79)						
8	2	7b	9b	5	88(72)						
9	2	7c	9c	5	57 (48)						
10	2	7d	 9d	7	(50)	20	3	7g	 10g	5	(58)
11	2	7e	 9e	6	67(58)	21	4	7a	 11a	4	75(68)
12	2	7f	 9f	4	81(71)	22	5	7a	12a	4	83 (74)
13	2	7g	 9g	5	(56)	23	5	7e	 12e	5	75(60)
14	3	7a	10a	4	75(66)	24 ^c	6	7a	13a	16	69(60)
15	3	7b	 10b	5	71(62)	25 ^c	6	7f	 13f	19	49(37)

^a ArCOCl (2.4 equiv) was used unless otherwise stated. ^b Determined by GC; isolated products between parentheses as an average of at least two independent runs. ^c ArCOCl (3.6 equiv).

compounds are the cyclotrimerization of acetylenic ketones⁹ as well as the Pd-catalyzed carbonylative coupling of triiodobenzene with triphenylindium.⁶

It is important to mention that the reactions carried out with 3- (**7d**) and 4-nitrobenzoyl chloride (**7g**) with different substrates could not be analyzed by CG/MS because the corresponding diketones did not elute from the column. These reactions were analyzed by NMR. In all these experiments there was detected, together with the desired diketone, the presence of trimethylstannylated nitrobenzophenone (10–20%) intermediates in the diarylation process. Although longer reaction times produced

a decreased amount of the intermediates, they also led to decomposition of the diketone. So, the reaction times specified in Table 2 (entries 4, 10, 13, 17, and 20) were optimal to avoid decomposition of the desired dinitrodiketones, which were isolated from the crude product by recrystallization. Furthermore, in the reaction carried out between **1** and **7c** (entry 3), the corresponding trimethylstannylated chlorobenzophenone (16%, CG/MS) was also detected, even after 36 h of heating.

In conclusion, the method proposed is an efficient catalyst-free straightforward route for di- and triarylation of an aromatic ring in a single step. Significantly, these products are known to be very valuable precursors for the synthesis of a variety of materials.^{3,10}

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Taking into account that the starting arylstannanes may be synthesized from the corresponding haloarenes,¹¹ phenols^{8b} or anilines,^{8a} the method proposed allows the regioselective substitution of a chloro, a hydroxy or an amino group on an aromatic ring, rendering specific di- and triketones in good global yields.

Nevertheless, one disadvantage of the method is the generation of trimethyltin chloride soluble in the aqueous phase during the workup of the reaction. Because of the environmental problems caused by the well-known toxicity of triorganotin residues, we considered really important to trap the Me₃SnCl generated. With this aim, the organotin chloride is removed in ca. 80%, by filtration as the insoluble trimethyltin fluoride (see the Experimental Section).

Experimental Section

Aryltins were prepared according to literature methods.^{8,11}

Representative Procedure for Aroyldestannylation. Preparation of 1,4-Phenylenebis(phenylmethanone) (8a; Table 2, Entry 1). In an oven-dried 25 mL heavy walled Schlenk tube fitted with a Teflon plug valve was added dropwise 0.28 mL (0.338 g, 2.40 mmol) of benzoyl chloride (**7a**) to a stirred solution of 1,4-bis(trimethylstannyl)benzene (**1**, 0.403 g, 1.00 mmol) in 1,2-dichlorobenzene (1.0 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 5 h (monitoring the disappearance of the stannane by TLC). A few drops of DMSO (0.2 mL) were added,¹² and the mixture was stirred at room temperature for a few minutes, diluted with dichloromethane (5 mL), and washed with water (3 × 5 mL). The resulting aqueous solution was reserved for further treatment

described below, and the organic layer was successively washed with a 10% (m/v) solution of sodium hydroxide, brine, and water, dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant solid was purified by flash chromatography on silica gel (hexane/AcOEt = 97:3) to provide **8a** as a white solid (0.200 g, 70%); mp 141–143 °C (lit.⁴ mp 158–160 °C); ¹H NMR (300 MHz, CDCl₃) δ 7.42 (t, 4H, *J* = 7.8 Hz), 7.46–7.57 (m, 2H), 7.67–7.79 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ 195.8 (CO), 140.6 (C), 136.9 (C), 132.8 (CH), 129.9 (CH), 129.5 (CH), 128.3 (C); EIMS *m/z* (rel intensity) 286 (M⁺, 55), 209 (62), 181 (12), 152 (15), 105 (100).

Disposal Method for Trimethyltin Chloride. The aqueous solution (~15 mL for 1.0 mmol scale reaction) was saturated with potassium fluoride. Diethyl ether (10 mL) was added, and the mixture was vigorously shaken. The precipitated trimethyltin fluoride¹³ (0.297 g, 81%) was removed by filtration at reduced pressure. The amorphous solid obtained was stored for future applications.¹⁴

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Supporting Information Available: General experimental procedures, compound characterization data, and copies of spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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