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Note

A catalyst-free synthesis of asymmetric diaryl ketones from aryltins

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Abstract

A series of diaryl ketones have been synthesized in good yields (40–78%) through the catalyst-free reaction of trimethylarylstannanes with aroyl chlorides in chlorobenzene as solvent. In addition, an attractive feature is that these reactions are completely regioselective making possible the synthesis of diarylketones which are not usually available under the influence of the directing forces of the substituents present in the aromatic ring. Also, the reaction conditions are mild enough to be applied to acid sensitive molecules.
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Keywords: Aryltin; Diarylketones; Aromatic acylation

1. Introduction

The acylation of aromatic systems is an important reaction in organic synthesis. Thus, a large number of related literature references have appeared since the first Friedel–Crafts reaction [1].

Organometallics are interesting starting materials for the synthesis of aromatic ketones and numerous efficient methods have been described in the last years [2]. Among them, the reaction of organotin compounds with acid chlorides have been widely used either in reactions catalyzed by Lewis acids [3] or in Pd-catalyzed cross-coupling reactions [4]. Although these reactions are efficient methods to form ketones in good yields, there are some disadvantages related with them. Thus, whereas in the first case the catalyst used cannot be easily recovered and a large amount of toxic waste is generated, in the latter case, although Pd catalysts could be recovered, it is usually necessary to find the appropriate catalytic protocol for each pair of reactants. Continuing with our studies related with the application of arylstannanes as intermediates in organic synthesis [5], we wish now to report a catalyst-free route to diarylketones based on the exceptional leaving group ability of the trimethylstannyl group in electrophilic aromatic substitutions.

2. Results and discussion

We synthesized a series of electronically diverse starting aryltrimethylstannanes (**1**–**8**, 60–100%) by reaction of either the corresponding trimethylarylammonium salts [6a] or diethyl aryl phosphates [6b] with trimethyltin anion in liquid ammonia. These routes of synthesis have two advantages: they allow the presence of sensitive substituents on the aromatic ring and the arylstannanes were obtained in very good global yields starting from economic and commercially available phenols or anilines, as is shown in Scheme 1.

The reaction of these arylstannanes with aroyl chlorides were carried out in chlorobenzene as solvent, at 130 °C. The general scheme of Eq. (1) applies for all the reactions studied:

$$\mathrm{Ar'SnMe_3} \xrightarrow[\substack{\mathrm{C_6H_5Cl}\\ 130\ ^\circ\mathrm{C}}]{\mathrm{ArCOCl}} \mathrm{ArCOAr'} + \mathrm{Me_3SnCl} \qquad (1)$$

The results obtained are summarized in Table 1. All the yields given are of isolated products by column chromatography (Silica gel).

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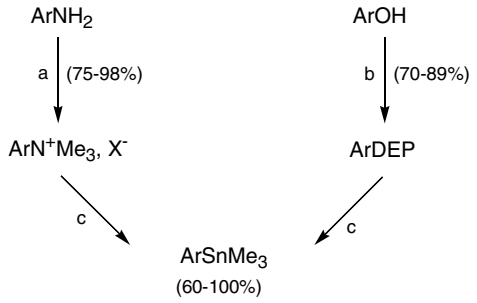
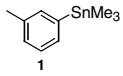
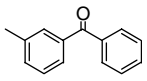
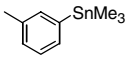
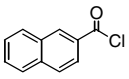
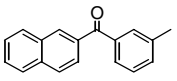
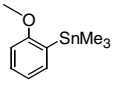
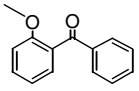
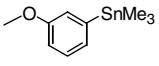
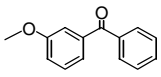
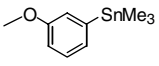
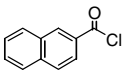
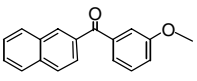
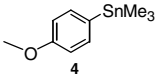
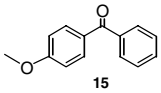
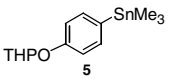
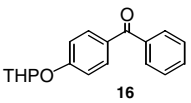


(a) MeI (or Me_2SO_4) 2,6-Lutidine, DMF, r.t.; (b) $HP(O)(OEt)_2$, NEt_3, CCl_4, r.t.; (c) $Me_3Sn^-Na^+$, NH_3 (l), hν.

Scheme 1.

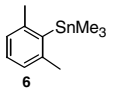
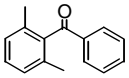
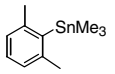
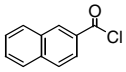
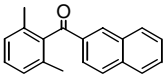
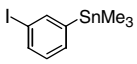
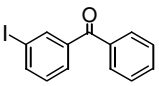
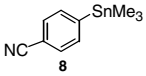
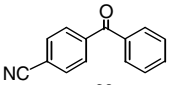
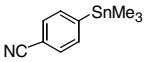
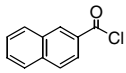
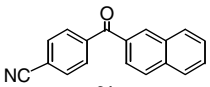
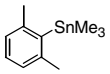
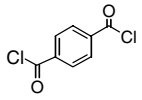
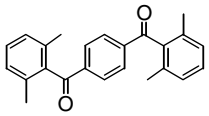
As seen from Table 1, arylstannane **1** reacted with benzoyl- and naphtoyl chloride in 60 h rendering the diarylketones **10** [7] and **11** in good yields (65% and 60%, respectively) (entries 1 and 2). Similar reactions carried out with arylstannanes **2**–**4** proceeded efficiently giving diarylketones **12** (78%), **13** (68%), **14** (65%) and **15** (70%) [7] (entries 3–6). It should be mentioned that the reaction conditions are mild enough to be applied to acid sensitive molecules such as **5**, leading to the corresponding ketone **16** (40%, 20 h), the protecting group remaining unchanged (entry 7) [8]. However, longer reaction times (40 h) led to **16** together with considerable amounts of secondary products that make difficult its purification.

Table 1
Reaction of trimethylaryltin compounds with aroyl chlorides[a]

Entry	$ArSnMe_3$	Aroyl chlorides	Product	Time (h)	Yield (%)[b]
1	 **1**		 **10**	60	65
2			 **11**	60	60
3	 **2**		 **12**	40	78
4	 **3**		 **13**	65	68
5			 **14**	90	65
6	 **4**		 **15**	60	70
7	 **5**		 **16**	20	40

(*continued on next page*)

Table 1 (*continued*)

Entry	$ArSnMe_3$	Aroyl chlorides	Product	Time (h)	Yield (%)[b]
8	 **6**		 **17**	49	71
9			 **18**	50	64
10	 **7**		 **19**	90	30
11	 **8**		 **20**	90	52
12			 **21**	90	58
13[c]			 **22**	90	64

[a] Substrate:ArCOCl = 1:1.2.
[b] Yields reported are based on isolated products.
[c] Substrate:ArCOCl = 1:0.6.

The more sterically hindered arylstannane **6** also reacted in effect with aroyl chlorides giving ketones **17** and **18** in good yields (71% and 64%, respectively) [9]. The results obtained with both compounds **2** and **6** (higher yields and lower reaction times) show that the electrophilic attack of arylstannanes is accelerated by the existence of neighboring groups on the arene system.

Arylstannanes **7** and **8** reacted with aroyl chlorides leading to the expected ketones in lower yields after longer reaction times. Thus, ketones **19**, **20** and **21** were obtained in 30% (90 h), 52% (90 h) and 58% (90 h), respectively. The decreased reactivity of these substrates is presumably due to the presence of electron-withdrawing groups such as iodine and nitrile, attached to the arene ring.

In addition, the reaction of arylstannane **6** with terephthaloyl chloride led to diketone **22** in 64% yield. This result enables us to say that this method could be also applied to the synthesis of triaryl diketones.

It should be mentioned that in all the experiments that we have carried out, it has been detected the presence of small amounts (not quantified) of *ipso*-protodestannylation products, probably this being due to the presence of small amounts of HCl that could not be eliminated from the aroyl chloride. These protodestannylation products are irrelevant compared with the yields of the diarylketones obtained.

It is important to note that all the reactions studied were regioselective and that they went, exclusively, through an *ipso*-aroyldestannylation independently whether the directing influences of the aryl substituents and the trimethylstannyl group are either matched (compounds **2**, **4** and **5**) or mismatched (compounds **1**, **3**, **7** and **8**). Even the known high directing force of MeO group could be completely overcompensated (compound **3**).

The high *ipso*-directing force shown by the trimethylstannyl group is probably due to the β-effect of the tin atom

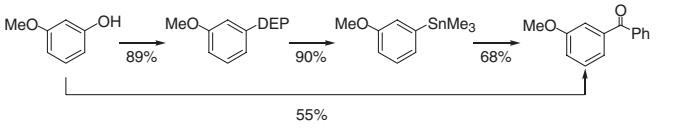
which makes easier the cleavage of an aryl group from the tin via an electrophilic *ipso*-substitution [10].

The method proposed is a straightforward and convenient route for the synthesis of unsymmetrical diaryl ketones. Nevertheless, one disadvantage is the generation of trimethyltin chloride (Eq. (1)) 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 Me_3SnCl generated. With this aim, the organotin chloride is removed in ca. 80%, by filtration as the insoluble trimethyltin fluoride (see Section 4).

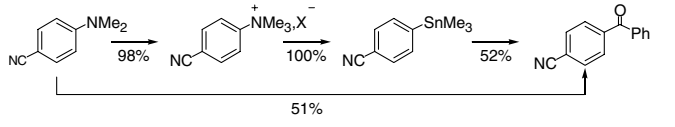
3. Conclusions

This paper reports a simple and direct route for the selective synthesis of asymmetric diaryl ketones. The dominant leaving characteristic of the trimethylstannyl group overcompensate the directing forces of groups such as Me, OMe, I, CN, making possible the aroylation of aromatic rings in otherwise not available positions under the influence of these groups. The method proposed has the advantage of enabling a high regioselective formation of diaryl ketones without employing a catalyst. Moreover, the reaction conditions are mild enough to be applied to acid sensitive molecules.

Taking into account that the starting arylstannanes have been synthesized in two steps from the corresponding phenols or anilines, i.e., generation of the corresponding diethyl aryl phosphates or trimethyl aryl ammonium salts, respectively, and trimethylstannylation, the method proposed allows the regioselective substitution of a hydroxy or an amino group on an aromatic ring, rendering specific diaryl ketones and triaryl diketones in good global yields. Two examples are sketched in the following equations:



(2)



(3)

It is important to note that although we were able to remove organotin residues from final products we could only trap 80% of the Me_3SnCl generated during the reactions. In order to decrease the level of pollution, we have started the study of an alternative route to obtain diaryl 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.

4. Experimental

The reactions were carried out under dry nitrogen using standard Schlenk techniques and syringes. All acid chlorides were commercially available and used as received except benzoyl chloride which was fractionally distilled under nitrogen before use. The aryltins were prepared according to the literature methods [5,6]. Chlorobenzene was dried by standard methods, distilled under dry nitrogen and stored over molecular sieves. The NMR spectra were recorded on a Bruker ARX 300 (300.1 MHz for ^1H, 75.5 MHz for ^{13}C) using $CDCl_3$ as solvent and $SiMe_4$ as internal reference. Mass spectra were obtained by use of a GC/MS HP 6890.

*4.1. Representative procedure for aroyldestannylation: preparation of 3-methoxybenzophenone (**13**; Table 1, entry 4)*

The reaction was carried out in a 25-mL one-necked round-bottomed flask equipped with a Teflon valve. To a stirred solution of 3-methoxyphenyl(trimethyl)stannane (**3**, 0.271 g, 1.00 mmol) in chlorobenzene (0.5 mL) was added benzoyl chloride (140 μL, 0.169 g, 1.20 mmol) dissolved in chlorobenzene (0.5 mL), dropwise. The reaction solution was heated at 130 °C (oil bath) for 65 h (monitoring the disappearance of the stannane by TLC). A few drops of DMSO (100 μL) were added [11], the mixture was diluted with dichloromethane (5 mL), stirred at r.t. for a few minutes and washed successively with a saturated solution of sodium carbonate, brine, and water, dried over sodium sulphate and concentrated in vacuo. Column chromatography on silica gel (230–400 mesh) of the crude mixture gave 0.144 g (68%) of 3-methoxyacetophenone (**13**) (using a mixture of 5% ethyl acetate in hexane). Spectroscopic data see Ref. [12].

4.2. Disposal method for trimethyltin chloride

The aqueous solution (~15 mL for 1.0 mmol scale reaction) was adjusted to ca. pH 1.0 with acid chloride and then saturated with potassium fluoride. Diethyl ether (10 mL) was added and the mixture was vigorously shaken. The precipitated trimethyltin fluoride [13] (0.145 g, 79%) was removed by filtration at reduced pressure. The amorphous solid obtained was stored for future applications.

Acknowledgements

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References

[1] J. March, Advanced Organic Chemistry, third ed., Wiley, 1985.
[2] K. Dieter, Tetrahedron 55 (1999) 4177.
[3] W.P. Neumann, H. Hillgärtner, K.M. Baines, R. Dicke, K. Vorspohl, U. Kowe, U. Nussbeutel, Tetrahedron 45 (1989) 951.
[4] J.W. Labadie, J.K. Stille, J. Am. Chem. Soc. 105 (1983) 6129.
[5] A.B. Chopa, G.F. Silbestri, M.T. Lockhart, J. Organomet. Chem. 690 (2005) 3865.
[6] (a) A.B. Chopa, M.T. Lockhart, G.F. Silbestri, Organometallics 20 (2001) 3358;
(b) A.B. Chopa, M.T. Lockhart, V.B. Dorn, Organometallics 21 (2002) 1425.
[7] Identified by comparison of spectroscopic data with those of the commercial reagent.
[8] GLC analysis of **16** resulted in cleavage of the protecting group.
[9] In conventional electrophilic aromatic substitution reactions it is difficult to effect substitution at a position between two methyl substituents *meta* to each other.
[10] (a) C. Dallaire, M.A. Brook, Organometallics 12 (1993) 2332;
(b) C. Eaborn, K.C. Pande, J. Chem. Soc. (1960) 1566.
[11] The coordinating ability of DMSO competes with the ketone improving the water solubility of trimethyltin chloride.
[12] Data for aryl ketones. For compound **11**, see: (a) R. Kakino, S. Yasumi, I. Shimizu, A. Yamamoto, Bull. Chem. Soc. Jpn. 75 (2002) 137;
(b) For compounds **12** and **13**, see: L.A. Liebeskind, J. Srogl, J. Am. Chem. Soc. 122 (2000) 11260;
(c) For compound **19**, see: G.A. Olah, Q. Wang, G. Sandford, G.K. Surya Prakash, J. Org. Chem. 58 (1993) 3194;
(d) For compound **20**, see: I. Kazmierski, M. Bastienne, C. Cosmini, J.-M. Paris, J. Périchon, J. Org. Chem. 69 (2004) 936;
(e) For compound **21**, see: J.H.P. Utley, G.G. Rozenberg, Tetrahedron 58 (2002) 5251;
(f) *Compound **14***: ^{1}H NMR: δ 8.24–7.01 (m, 11H); 3.78 (s, 3H). ^{13}C NMR: δ 195.4 ($C_{carbonyl}$), 158.7 (C_{aryl}), 138.3 (C_{aryl}), 134.3 (C_{aryl}), 133.9 (C_{aryl}), 131.3 (C_{aryl}), 130.8 (CH_{aryl}), 128.4 (CH_{aryl}), 128.5 (CH_{aryl}), 127.3 (CH_{aryl}), 127.2 (CH_{aryl}), 126.8 (CH_{aryl}), 125.8 (CH_{aryl}), 124.7 (CH_{aryl}), 121.8 (CH_{aryl}), 117.8 (CH_{aryl}), 113.4 (CH_{aryl}), 54.5 (CH_3); MS (*m*/*z*, relative intensity): 262 (75, M^+), 231 (14), 155 (100), 127 (75), 92 (11), 77 (21);
(g) *Compound **16***: ^{1}H NMR: δ 7.79–6.76 (m, 9H), 5.46 (m, 1H), 3.81 (m, 1H), 3.48 (m, 1H), 1.88–1.32 (m, 6H). ^{13}C NMR: δ 196.5 ($C_{carbonyl}$), 170.0 (C_{aryl}), 138.9 (C_{aryl}), 138.7 (C_{aryl}), 133.3 (CH_{aryl}), 132.4 (CH_{aryl}), 130.1 (CH_{aryl}), 128.6 (CH_{aryl}), 115.7 (CH_{aryl}), 95.2 (CH), 63.4 (CH_2), 31.1 (CH_2), 25.8 (CH_2), 20.1 (CH_2);
(h) *Compound **17***: ^{1}H NMR: δ 7.71 (m, 2H), 7.45 (m, 1H), 7.32 (m, 2H), 7.11 (m, 1H), 6.95 (m, 2H), 2.00 (s, 6H). ^{13}C NMR: δ 200.7 ($C_{carbonyl}$), 140.1 (C_{aryl}), 137.5 (C_{aryl}), 134.5 (C_{aryl}), 134.0 (CH_{aryl}), 129.8 (CH_{aryl}), 129.3 (CH_{aryl}), 129.1 (CH_{aryl}), 128.0 (CH_{aryl}), 19.7 (CH_3). MS (*m*/*z*, relative intensity): 210 (85, M^+), 209 (100), 192 (38), 165 (16), 133 (50), 105 (64), 77 (88);
(i) *Compound **18***: ^{1}H NMR: δ 8.06 (m, 1H), 7.91 (m, 1H), 7.80–7.71 (m, 3H), 7.48–7.35 (m, 2H), 7.16 (m, 1H), 6.99 (m, 2H), 2.04 (s, 6H).^{13}C NMR: δ 200.7 ($C_{carbonyl}$), 140.3 (C_{aryl}), 136.4 (C_{aryl}), 135.0 (C_{aryl}), 134.8 (C_{aryl}), 133.2 (C_{aryl}), 132.4 (CH_{aryl}), 130.2 (CH_{aryl}), 129.3 (CH_{aryl}), 129.22 (CH_{aryl}), 129.20 (CH_{aryl}), 128.3 (CH_{aryl}), 128.1 (CH_{aryl}), 127.21 (CH_{aryl}), 124.6 (CH_{aryl}), 19.8 (CH_3); MS (*m*/*z*, relative intensity): 260 (100, M^+), 259 (75), 242 (46), 228 (12), 215 (19), 155 (28), 127 (76), 105 (29), 77 (40);
(j) *Compound **22***: ^{1}H NMR: δ 7.78 (s, 4H), 7.18 (m, 2H), 6.99 (d, 4H, $^{3}J_{(H,H)}$ 7.4 Hz), 2.04 (s, 12H). ^{13}C NMR: δ 200.2 ($C_{carbonyl}$), 140.9 (C_{aryl}), 139.5 (C_{aryl}), 134.6 (C_{aryl}), 130.1 (CH_{aryl}), 129.5 (CH_{aryl}), 128.1 (CH_{aryl}), 19.8 (CH_3). MS (*m*/*z*, relative intensity): 342 (95, M^+), 327 (12), 209 (100), 194 (27), 165 (18), 132 (90), 105 (59), 77 (30).
[13] Organotin fluorides are relatively benign compounds. They are high melting, nonvolatile, insoluble (in both organic solvents and in water) and not easily absorbed through the skin, therefore the risks of organotin fluorides are less than those of other organotins: J.E. Leibner, J. Jacobus, J. Org. Chem. 44 (1979) 449.