Indium-mediated aroylation *vía* arylstannanes. Theoretical and experimental study.

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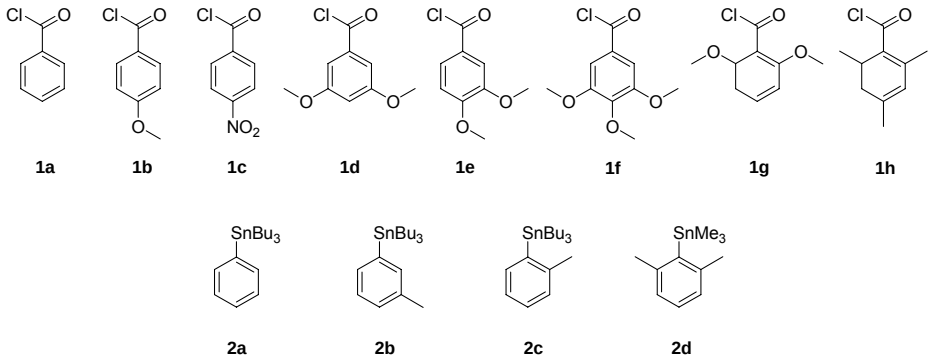
Introduction

Ketones are vital building blocks in organic synthesis as well as an important functionality found in pharmaceutical compounds. The Friedel-Crafts (F-C) acylation of aromatic compounds is the most frequent route for the synthesis of aromatic ketones.[1] However, it has intrinsic limitations such as 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 they are not recovered. Arylstannanes are valuable reagents for the regiospecific generation of C-C bonds. In the last years, we have been involved in the synthesis of arylstannanes[3] as well as in their application as intermediates in organic synthesis.[4] In recent years, the development of indium-mediated synthetic methods has grown up in the literature due to the special properties of indium metal.[5] 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 bulky aroyl chlorides with bulky arylstannanes applied to the synthesis of hindered benzophenones.[4e] In order to determine the scope of this reaction for the general synthesis of benzophenones, we studied the reaction, under similar conditions, of benzoyl chlorides **1a-h** with arylstannanes **2a-d**.



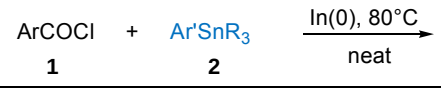
We now report the unexpected experimental results and a theoretical study of this reaction.

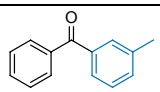
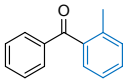
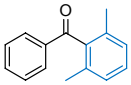
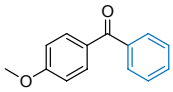
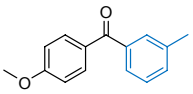
Results and Discussion

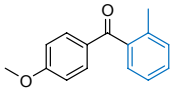
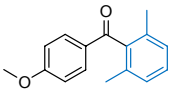
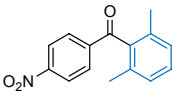
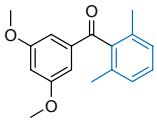
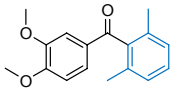
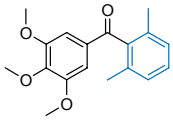
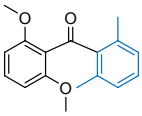
We initiated our studies with the solvent-free, indium promoted reaction between benzoyl chloride (**1a**) and tributylphenylstannane (**2a**) as a model system. Unexpectedly, after long reaction times (24 h), even traces of the desired ketone were not detected although working at higher temperatures (50-100°C) or employing an excess of **1a**.

Next, and based on our previous experience where arylstannanes containing electron-releasing substituents were proved to be adequate substrates,[4e] we carried out a series of reactions between **1a** and arylstannanes **2b**, **2c** and **2d** (Table 1, entries 1 to 3). The results obtained showed that working at 80ºC (24 h), meanwhile **2b** was unreactive, the reaction of **2c** and **2d** with **1a** rendered the corresponding ketones **3ca** and **3da**, although in low yields (traces and 25%, respectively). It should be mentioned that **3da** was obtained together with the undesired isomeric ketone (5%) and that in these reactions starting substrate was partially recovered. On the other hand, after 5 h, the reaction of arylstannanes **2a** to **2d** with (4-methoxy)benzoyl chloride (**1b**) gave the corresponding ketones, although in low yields (traces up to 20%) (Table 1, entries 4 to 7). In contrast, the reactions carried out with (4-nitro)benzoyl chloride (**1c**) were negative even after 72 h (Table 1, entry 8).

Table 1. Indium-mediated reactions of arylstannanes with aroyl chlorides



Entry[a]	ArCOCl	Ar'SnR$_3$	Time (h)	ArCOAr'	Yield (%)[b]
1	**1a**	**2b**	24	 **3ab**	0
2	**1a**	**2c**	24	 **3ac**	traces
3	**1a**	**2d**	24	 **3ad**	25[c]
4	**1b**	**2a**	5	 **3ba**	traces
5	**1b**	**2b**	5	 **3bb**	4

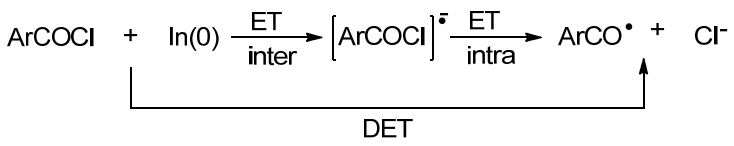
6	**1b**	**2c**	5	 **3bc**	9
7	**1b**	**2d**	5		20
8	**1c**	**2d**	72	 **3cd**	0
9	**1d**	**2d**	2	 **3ed**	6
10	**1e**	**2d**	2	 **3ed**	48[d]
11	**1f**	**2d**	2	 **3fd**	32[e]
12[f]	**1g**	**2d**	2	 **3gd**	55

[a] All reactions were conducted in solventless conditions using 1.2 equiv of **1**, 1.0 equiv of **2** and 1.0 equiv of indium metal. [b] Determined by GC (using tetradecane as internal standard). [c] Together with the regioisomer (5 %). [d] Together with the regioisomer (4.5 %). [e] Together with the regioisomer (10 %). [f] Ref. 4a.

These preliminary results showed that the nature of the benzoyl chloride is an important parameter in these reactions and that electron releasing groups attached to the aromatic ring increased its reactivity, in agreement with our previous results.[4e]

Based on these outcomes we considered interesting to study the reactivity of arylstannane **2d** towards different commercially available benzoyl chlorides containing two or three electron-releasing groups (ERGs) in diverse positions, such as (3,5-dimethoxy)benzoyl chloride (**1d**), (3,4-dimethoxy)benzoyl chloride (**1e**) and (3,4,5-trimethoxy)benzoyl chloride (**1f**). The reactions were quenched at 2 h, in order to compare results with those we have formerly reported.[4e] The reactions were positive and ketones **3dd**, **3ed** and **3fd** were obtained in 6%, 48% and 32% yield, respectively (Table 1, entries 9 to 11). In the above mentioned work we have informed the synthesis of the bulky ketone **3gd** (55%; Table 1, entry 12) under a similar protocol.[4e] So, it is evident that the effectiveness of the reaction depends mainly on the relative position of the ERGs in the aromatic ring rather than their number. Thus, isomers **1e** (3,4-dimethoxy) and **1g** (2,6-dimethoxy) are more reactive than isomer **1d** (3,5-dimethoxy); moreover, **1e** and **1g** are more reactive than **1f** (3,4,5-trimethoxy).

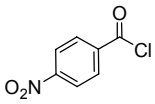
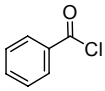
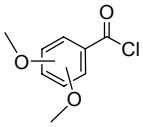
These observations together with the fact that the reactions proceed through an intermolecular electron transfer (ET-inter) from In(0) to the aroyl chloride generating an acyl radical (Scheme 1),[4e] prompted us to study in more detail the electron transfer process involved, using density functional theory (DFT) calculations. For this purpose, we theoretically study the neutral acyl chlorides and the corresponding radical anions of compounds **1a**, **1c** and the dimethoxybenzoyl chlorides isomers **1d** and **1g** as representative compounds. The ab initio calculations were performed with the B3LYP[6] DFT[7] functional and the 6-31+G* basis set, which is known to be an appropriate methodology for the theoretical study of the electronic properties of radical anions.[8]



Scheme 1

As expected, LUMO MOs of the neutral benzoyl chlorides showed differences in energy (Table 2).

Table 2. LUMO MOs energy for different benzoyl chlorides

ArCOCl	 **1c**	 **1a**	 **1d,g**
LUMO energy (eV)	-3.76	-2.45	~-2.00

The presence of an electron-withdrawing group attached to the aromatic ring (**1c**) increases the stability of the π-system and lowers its LUMO, favoring the electron transfer (ET-inter) process by increasing the electron affinity of the substrate. The unreactivity of derivative **1c** is related to the distribution of spin density, a relevant factor for reactions that proceed through ET processes.[9] Once the corresponding radical anion is generated, the unpaired electron is located mainly on the nitro function instead on the carbon center of the acyl group (Figure 1), therefore, even when the **1c** radical anion was efficiently generated, the fragmentation does not take place and the acyl radical is not generated.

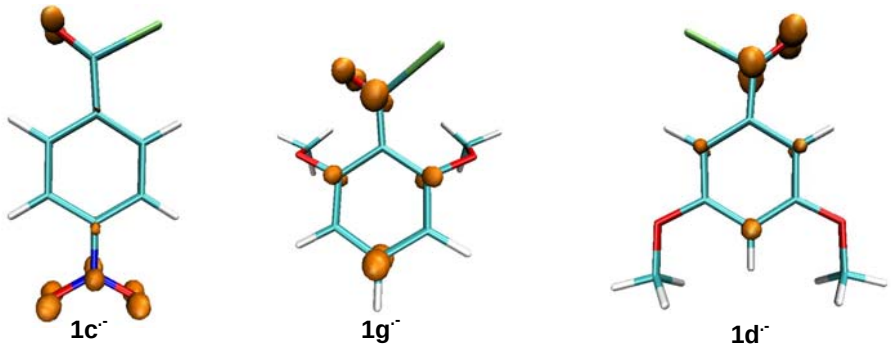


Figure 1. Gas phase B3LYP/6-31+G* spin density (orange) for **1c**$^{-\cdot}$, **1g**$^{-\cdot}$ and **1d**$^{-\cdot}$

The situation for isomers **1d** and **1g** is different; although both have, as expected, similar electronic affinities, their reactivities are completely different. Thus, while **1g** gives the ketone in a good yield (55%), **1d** gives the product in only 6% yield. Taking this in account, we analyzed the corresponding radical anions as intermediates in the substitution process. As can be seen from Figure 1, there are no differences in the unpaired electron of both radical anions. Considering that the formation of the acyl radical is possible through an intramolecular dissociative ET (intra-DET) from the π system to the σ^* CO-Cl bond in the benzoyl radical anion (Scheme 1), we evaluated the potential energy surfaces (PES) for the dissociation of both intermediates. Meanwhile the radical anion **1d** dissociates with high activation energy (7 Kcal/mol, Figure 2), the fragmentation takes place without activation energy for the radical anion **1g**.

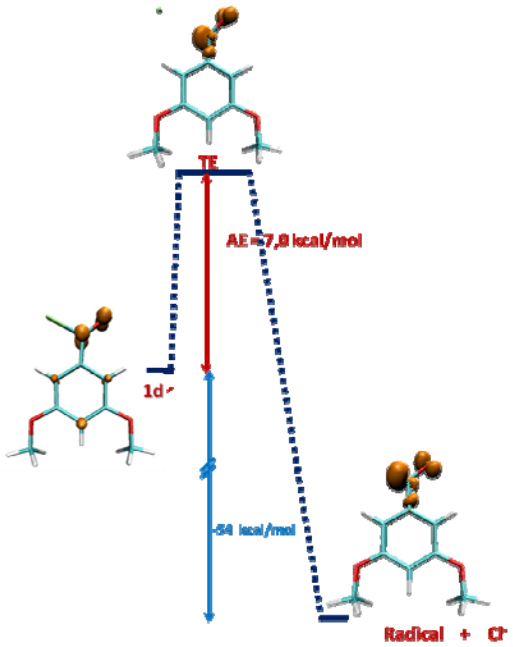


Figure 2. Gas Phase B3LYP/6-31+G* potential energy profile for dissociation of **1d**$^{-\cdot}$.
Spin densities are shown (orange)

This means that, for the derivative **1d** the formation of the benzoyl radical occurs exothermically through a radical anion intermediate, while for the derivative **1g** the corresponding radical is generated faster after a spontaneous dissociative electron transfer (DET) (Scheme 1). As can be seen from Figure 3, the radical anion **1g** shows an out of plane distortion from the optimal sp^2 dihedral angle Cl-CO-C1-C2 from 0° to -20.5°, probably due to steric repulsion with the *ortho*-methoxyl substitutents. This distortion could facilitate the cleavage of this radical anion,[10] being more efficient the ET process since the spatial geometric arrangement of the interacting π and σ^* orbitals is more appropriate.

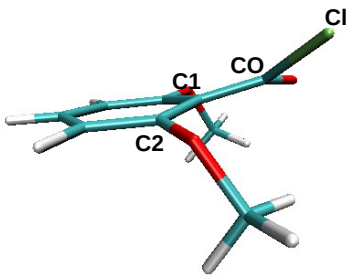


Figure 3. B3LYP/6-31+G* geometry of **1g**$^{-\cdot}$

Conclusions

At present, the results obtained show that the efficiency of the solvent-free, indium-promoted reaction of aroyl chlorides with arylstannanes for the synthesis of benzophenones, depends not only on the electronic nature of the substituents but, specially, on their relative position on the aromatic ring of the benzoyl chloride. On the other hand, DFT calculations have shown to be a successful approach for studying the ET process of a series of benzoyl chlorides as well as to explain the experimental results.

Experimental Section

General Experimental Methods

All reactions were carried out under a dry nitrogen atmosphere. Acid chlorides were commercially available and fractionally distilled under nitrogen or recrystallized from hexane before use. Aryltributylstannanes **2a**-**c**, were prepared by transmetallation of the appropriate Grignard reagents with tributyltin chloride in anhydrous THF. Aryltrimethylstannane **2d** was obtained from the corresponding commercial aryl chlorides by photostimulated reaction with Me_3SnNa in liquid ammonia, according to the literature procedures.[11]

Identity of products were established using a GC/MS instrument (HP5-MS capillary column, 30 m × 0.25 mm × 0.25 μm) equipped with 5972 mass selective detector operating at 70 eV (EI). Program: 50 °C for 2 min with increase 10 °C/min to 280 °C. For gas-liquid chromatography (GLC) an instrument equipped with a flame-ionization detector and a HP5 capillary column (30 m × 0.25 mm × 0.25 μm) was used.

General Procedure for Indium-Mediated Reactions

In a flame dried Schlenk tube (fitted with a teflon plug valve) 1.2 mmol of acid chloride **1** was added to a stirred mixture of 1.0 mmol of arylstannane **2** and indium powder (1.0 mmol) under a nitrogen gas stream. The system was purged with nitrogen by means of three pump-fill cycles and then the heterogeneous reaction mixture was stirred at 80 ºC (oil bath) for the time indicated in Table 1. After addition of 10 % (m/v) solution of NaOH (2 mL) and 10 µL of tetradecane, the mixture was stirred at room temperature for 15 min and then diluted with DCM (5 mL). The organic phase was successively washed with water and brine, dried over Na_2SO_4, filtered and analyzed by GC and GC/MS

Computational Procedure

The calculations were performed with Gaussian03.[12] The initial conformational analysis of selected compounds was performed with the semiempirical AM1 method. The geometry of the most stable conformers thus obtained was used as starting point for the B3LYP studies of the corresponding benzoyl chloride and their radical anions. The zero point energy corrections were made at the 6-31+G* level for the thermodynamic quantities. The exploration of the potential surface was carried out varying the selected coordinate with full optimization for the remainder degrees of freedom. The characterization of all stationary points was done by Hessian matrix calculations of geometries obtained with full optimization for a minimum and by using the TS methodology for a transition state. The zero point energy corrections were made at the 6-31+G* level for the thermodynamic quantities. Figures were built with the GaussView program using a spin density isosurface of 0.02.

Acknowledgements

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