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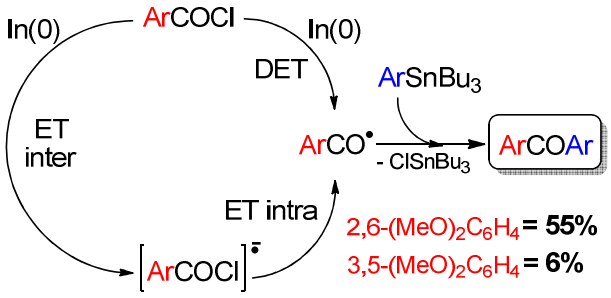

A DFT analysis was performed with the aim to explaining the narrow scope of the indium-promoted reaction of aroyl chlorides with arylstannanes.

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ARTICLE TYPE

Experimental and DFT study on the indium-mediated synthesis of benzophenones *via* arylstannanes†

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Experimental results of the solvent-free, indium-promoted reaction of aroyl chlorides with arylstannanes showed a narrow scope; its efficiency depends both on the extent of methylation in the latter and on the nature, number and position of the substituents in the former. With the purpose of explaining experimental results, a theoretical analysis with DFT methods was performed for a set of selected cases.

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] focused, especially, in the development of new procedures for the regiospecific synthesis of aryl ketones through catalyst-free processes.[4b-e]

The advance of indium-mediated synthetic methods has grown up in the recent literature due to the special properties of indium metal.[5] 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, in the synthesis of severely hindered benzophenones;[4e] moreover, we have also established that it is a promoter of the solvent-free reaction of alkanoyl chlorides with arylstannanes, in the synthesis of primary, secondary and tertiary alkyl aryl ketones.[4h] The reactions are carried out under mild and neutral conditions, being their striking advantages (i) the use of no solvent, (ii) readily available, non-toxic and reusable metal catalyst; (iii) accessible substrates and reactants and (iv) the specificity of the reaction. On the latter point, it is worth noting that, whether the reaction proceeds via a free-radical or ionic mechanism, the arylstannane plays a key role in regards to the regioselectivity of the benzophenones synthesis. The high *ipso* reactivity makes it possible to carry out aromatic substitution under mild conditions overriding the normal directive effect of substituents. This is ascribed mainly to the stabilization of the cyclohexadienyl radical or cation intermediates by hyperconjugation between the singly occupied or unoccupied 2p orbital and the β-C-Sn bond (often referred as β-effect). Furthermore, unlike the corresponding homolytic substitution of hydrogen, the stannyl radical should be rapidly lost from the cyclohexadienyl intermediate without the need for any oxidant.[6] In this connection we sought to establish the scope of this solvent free approach, with the ultimate goal of developing a general method for the synthesis of benzophenones. Thus, we initiated a systematic study of the reaction between a series of representative benzoyl chlorides (Figure 1, **1a-g**) with a series of arylstannanes (Figure 1, **2a-d**) and herein, we report the unexpected experimental results and a possible theoretical interpretation of this reaction.

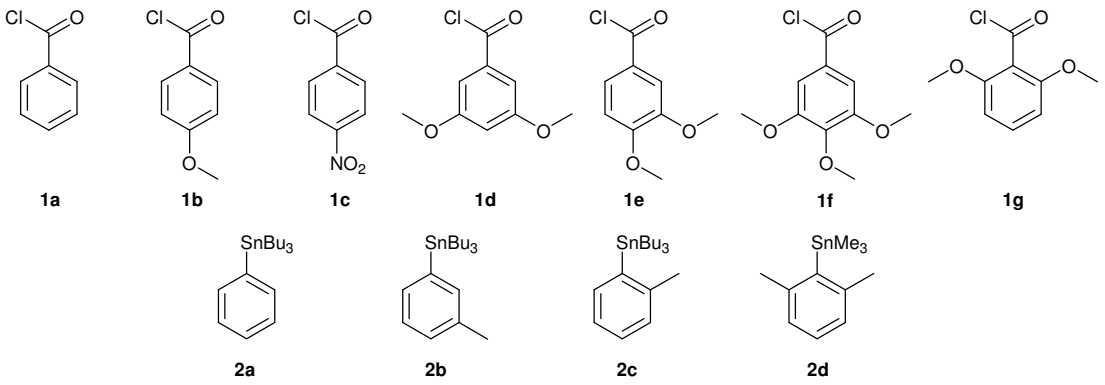


Figure 1. Starting materials: benzoyl chlorides and arylstannanes

Results and Discussion

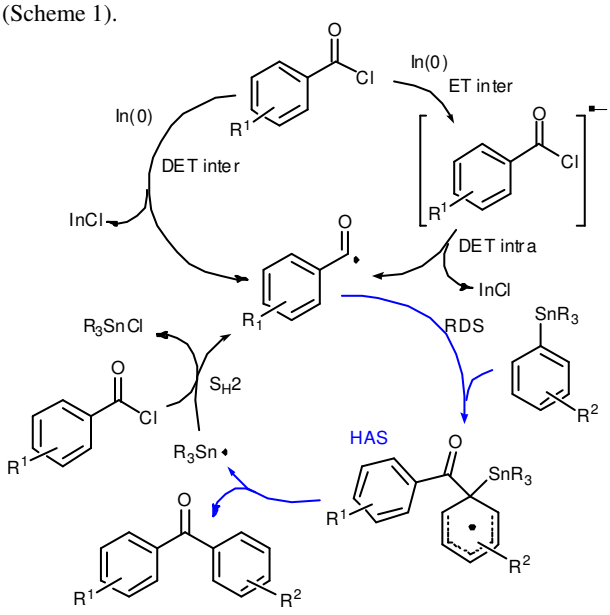
We initiated our studies with the reaction between benzoyl chloride (**1a**) and tributylphenylstannane (**2a**) as a model system. Unexpectedly, after long reaction times (24 h), even traces of the desired ketone were not detected although working at higher temperatures (50-100°C) or employing an excess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

Next, and based on our previous experience where arylstannanes containing electron-releasing substituents were proved to be adequate substrates under this protocol,[4e,h] 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),[7] meanwhile **2b** was unreactive, the reaction of **2c** and **2d** with **1a** yielded the corresponding ketones **3ac** and **3ad**, although in really low yields (traces and 20%, respectively), and substantial amounts of reactant were recovered. It should be mentioned that **3ad** was obtained together with the undesired isomeric ketone (2,4-dimethylphenyl)phenyl methanone (5%), product of the direct aroylation of the aromatic ring followed by protodestannylation. Likewise, the reaction of arylstannanes **2a** to **2d** with (4-methoxy)benzoyl chloride (**1b**) gave the corresponding ketones, (traces up to 25%) (Table 1, entries 4 to 7). In contrast, the reaction of **2d** with (4-nitro)benzoyl chloride (**1c**) was negative even after 72 h (Table 1, entry 8).

These preliminary results showed that the nature of the benzoyl chloride is an important parameter in these reactions and that a π-electron releasing group attached to the aromatic ring increased its reactivity (entries 1-3 *vs* 5-7 and entry 7 *vs* 8). Furthermore, the reactions carried out with arylstannane **2d** gave better yields (entries 3 and 7).

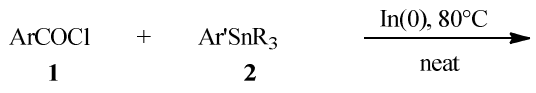
Based on these outcomes we considered it interesting to study the reactivity of arylstannane **2d** towards different commercially available benzoyl chlorides containing two or three methoxy groups in diverse positions, such as (3,5-dimethoxy)benzoyl chloride (**1d**), (3,4-dimethoxy)benzoyl chloride (**1e**) and (3,4,5-trimethoxy)benzoyl chloride (**1f**). The reactions, which were quenched at 2 h in order to compare results with those we have formerly reported,[4e] gave the corresponding ketones **3dd**, **3ed** and **3fd** with 6%, 48% and 32% yield, respectively (Table 1, entries 9 to 11). In a previous 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 methoxy groups 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) and even than **1f** (3,4,5-trimethoxy).

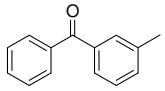
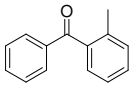
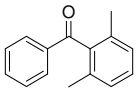
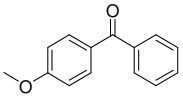
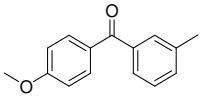
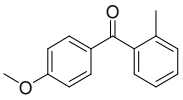
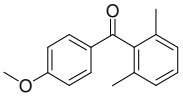
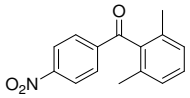
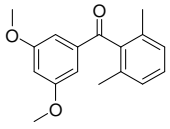
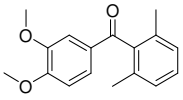
It is important to note that a control experiment showed that no reaction occurred in the absence of In(0). Besides, it is known that, because of its low first ionization potential, In(0) is capable of promoting single-electron transfer (SET) processes.[8] To prove whether acyldestannylations proceeded through a polar or a free radical pathway, we performed the reaction of **1f** and **2d** in the presence of 0.5 equiv of di-*tert*-butyl nitroxide (DTBN) as radical scavenger. Compared with a blank reaction, we noticed that the addition of DTBN had a dramatic retardation effect and only traces of ketone **3fd** were detected recovering the starting substrate. On the basis of these results, we believe that the reaction proceeds initially through a SET from In(0) to the aroyl chloride with generation of an acyl radical and In(I) chloride salt. The acyl radical thus formed reacts with the arylstannane through a homolytic *ipso* aromatic substitution affording the ketone (Scheme 1).[4e] The high *ortho*-selectivity make it reasonable to speculate that the formation of the cyclohexadienyl radical intermediate is the rate determining step (RDS) which is conditioned by the degree of fragmentation of the acyl radical anion and the reactivity of the corresponding acyl radical (Scheme 1).

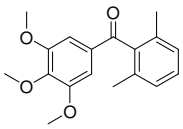
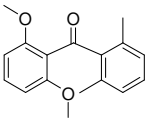


Scheme 1

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



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**	20[c]
4	**1b**	**2a**	24	 **3ba**	traces
5	**1b**	**2b**	24	 **3bb**	4
6	**1b**	**2c**	24	 **3bc**	9
7	**1b**	**2d**	24	 **3bd**	25
8	**1c**	**2d**	72	 **3cd**	0
9	**1d**	**2d**	2	 **3dd**	6[d]
10	**1e**	**2d**	2	 **3ed**	48[d,e]

11	**1f**	**2d**	2	 **3fd**	32[d,f]
12[g]	**1g**	**2d**	2	 **3gd**	55
13[g,h]	**1g**	**2d**	2	**3gd**	49

[a]All reactions were conducted at 80 °C (oil bath) 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-MS (using tetradecane as internal standard). [c]Together with the regioisomer [(2,4-dimethylphenyl)phenyl methanone, 5 %]. [d]Traces of mesitylene were detected (GC-MS) and large amounts of unreacted starting materials were recovered. [e]Together with the regioisomer [(3,4-dimethoxyphenyl)(2,4-dimethylphenyl)methanone, 4 %]. [f]Together with the regioisomer [(3,4,5-trimethoxyphenyl)(2,4-dimethylphenyl)methanone, 10 %]. [g]Ref. 4e. [h]Performed with 0.2 equiv of indium metal.

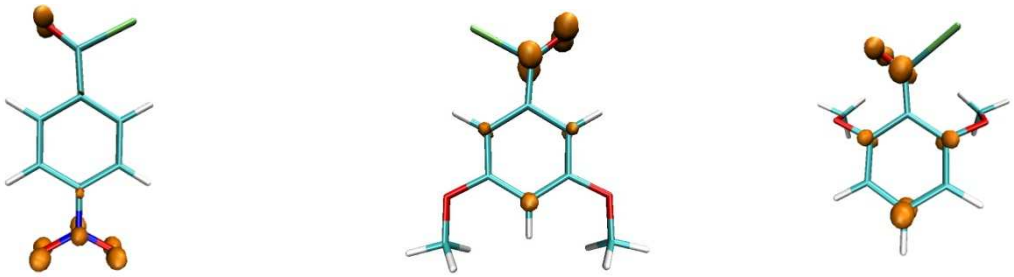


Figure 2. Gas phase B3LYP/6-31+G* spin density (orange, isosurface of 0.02) for **1c**•-, **1d**•- and **1g**•-

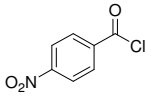
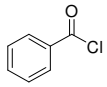
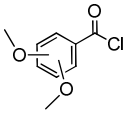
The unexpected results together with the fact that the reactions proceed through an electron transfer (ET) pathway generating an acyl radical (Scheme 1), prompted us to study, in more detail, the ET process involved using density functional theory (DFT) calculations. For this purpose, we simplified the reactive system and theoretically studied 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 density functional theory[9] calculations were performed with the B3LYP[10] functional and the 6-31+G* basis set, which is known to be an appropriate methodology for the theoretical studies of electron affinities[11] and electronic properties of radicals[12] and radical anions.[13]

Adiabatic electron affinity (AEA) can be used as a magnitude of the reactivity of a molecule toward a SET process. Table 2 shows AEA of the neutral benzoyl chlorides, obtained as the difference in the energies between the neutral molecule and the radical anion with full geometry optimization of both species, including the zero point energy (ZPE) corrections (eqn. 1). [11b-d] As expected, benzoyl chlorides showed differences in energy

AEA = E(optimized neutral) – E(optimized radical anion) **(1)**

The presence of an electron-withdrawing group attached to the aromatic ring (**1c**) increases the stability of the π-system.[14] Evidence of this is the shortening of the C-NO_2 bond in the radical anion (1.40 Å) with respect to the neutral (1.48 Å).[13a; 14b]

Table 2. Adiabatic electron affinities energy (B3LYP/6-31+G*)[16] for different benzoyl chlorides.

Benzoyl chlorides	Adiabatic EAs energy (eV)
 **1c**	2.37
 **1a**	0.98
 **1d**	0.89
1g	0.58

Thus, the electron transfer (ET-inter) process is favored, by increasing the adiabatic electron affinity of the substrate. The unreactivity of derivative **1c** is related to the distribution of spin density,[13a,d;14b] a relevant factor for reactions that proceed through ET processes.[15] Unlike radical anions **1d** and **1g**, once the corresponding radical anion is generated in **1c**, the unpaired

electron is located mainly on the nitro function rather than on the carbon center of the acyl group (Figure 2); therefore, even when the **1c** radical anion was efficiently generated, the expected fragmentation does not take place and the acyl radical is not generated.

The situation for isomers **1d** and **1g** is different; although both have, as expected, similar electron affinities, their behavior towards the most reactive arylstannane **2d** is 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, the goal of this computational study is to analyze the corresponding radical anions, as intermediates in the substitution, bearing in mind the spin density and fragmentation process as possible factors responsible for the observed differences. As can be seen from Figure 2, there are no differences in the unpaired electron of both radical anions. With respect to the fragmentation process, once the neutral acyl chloride gain an electron from In(0) (inter-ET), the reaction may follow two mechanisms:[13a,14b] i. a concerted dissociative pathway where the CO-Cl bond breaks as the benzoyl radical anion is being formed (inter-DET); ii. a stepwise mechanism, where takes place an intramolecular dissociative ET (intra-DET) from the π system to the σ* CO-Cl bond once the benzoyl radical anion is formed (Scheme 1). Considering that, we evaluated the potential energy surfaces (PES) for the dissociation of both intermediates. Our results indicate that the formation of the benzoyl radical from **1d** occurs exothermically (stepwise mechanism) through a radical anion intermediate, being the activation energy 8.1 kcal/mol[17] (Figure 3). On the other hand, the fragmentation of the radical anion **1g** takes place without activation energy generating the corresponding radical by a spontaneous dissociative electron transfer (inter-DET) (Scheme 1).

As can be seen from Figure 4, the main geometric difference between both radical anions isomers is that radical anion **1g** shows an out of plane distortion from the optimal sp^2 dihedral angle Cl-CO-C^1-C^2 from 0° to -20.5°,[18] probably due to steric repulsion with the *ortho*-methoxy substitutents. The SOMO MO shows that this distortion could facilitate the cleavage of this radical anion,[14b;19] being more efficient the intra-DET process since this spatial geometric arrangement increases the interaction and the overlap of the π and σ* orbitals in comparison to the planar radical anion **1d**.

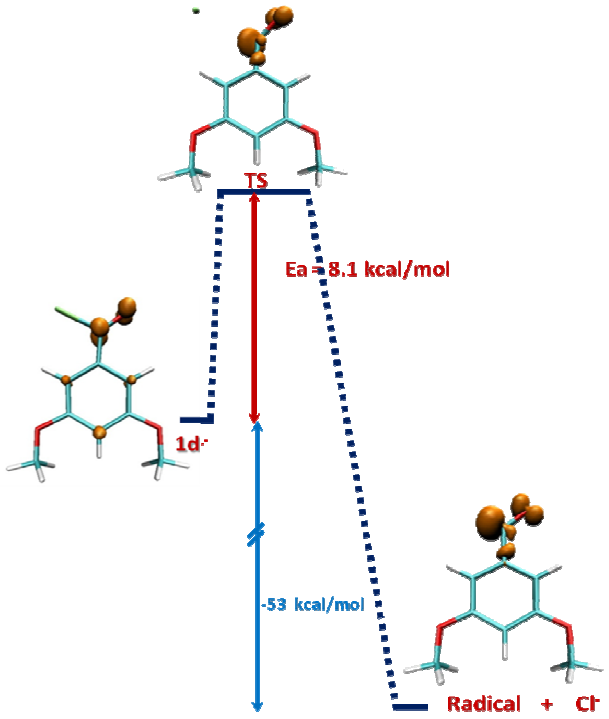
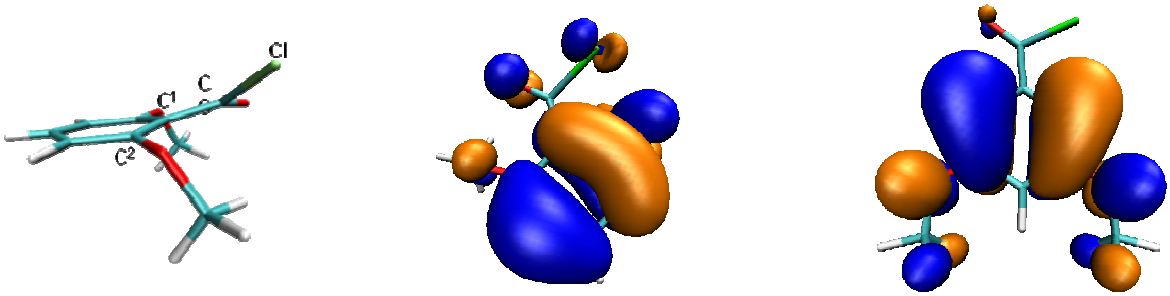


Figure 3. Gas Phase B3LYP/6-31+G* potential energy profile for dissociation of **1d**·⁻.[20] Spin densities are shown in orange (isosurface of 0.02)



1g·⁻ **1g**·⁻ **1d**·⁻

Figure 4. B3LYP/6-31+G* geometry of **1g**·⁻ and SOMO MOs (orange and blue, isosurface of 0.02) of **1g**·⁻and **1d**·⁻

Conclusions

Despite the limited scope of this methodology, our results are a contribution to the research related to the action of metallic indium as a promoter of free-radical reactions in organic synthesis. We have observed that the effectiveness of the synthesis of benzophenones, through the indium-promoted solvent-free reaction of aroyl chlorides with arylstannanes, depends not only on the extent of methylation in the latter but, in a very peculiar way, on the nature, number and position of the substituents in the former. A good agreement between DFT calculation and the experimental results was found for the analyzed cases. In this way the B3LYP functional and the 6-31+G* basis set demonstrated to be an adequate and computationally economic methodology for studying reactive systems that imply radicals and radical anions involved in ET processes.

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 chloride by photostimulated reaction with Me_3SnNa in liquid ammonia, according to the literature procedures.[21]

The products were identified unambiguously by comparing their retention times and mass spectra with those of authentic compounds obtained by known procedures,[4e] 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.

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.

(2-Methylphenyl)phenylmethanone (3ac).[22] MS-EI, m/z (% rel. intensity, ion): 196 (57, M^+), 195 [89, (M^+–H)], 178 [16, (M^+–H_2O)], 119 [30, (M^+–Ph)], 105 [29, (M^+–Tol)], 91 (56), 77 (100).

(2,6-Dimethylphenyl)phenylmethanone (3ad).[23] MS-EI, *m/z* (% rel. intensity, ion): 210 (33, M^+), 209 [40, (M^+–H)], 195 [20, (M^+–Me)], 133 [23, (M^+–Ph)], 105 [42, (M^+–$C_6H_4Me_2$], 77 (100).

(4-Methoxyphenyl)phenylmethanone (3ba).[21] MS-EI, *m/z* (% rel. intensity, ion): 212 (31, M^+), 135 [100, M^+–Ph)], 105 [12, (M^+–Ans)], 92 (22), 77 (54).

(4-Methoxylphenyl)(3-methylphenyl)methanone (3bb).[24] MS (EI, 70eV) *m/z* (% rel. intensity, ion): 226 (27, M^+), 211 [6, M^+–Me)], 135 [100, (M^+–Tol)], 119 [3, M^+–Ans)], 92 (25), 77 (22).

(4-Methoxylphenyl)(2-methylphenyl)methanone (3bc).[21] MS (EI, 70eV) *m/z* (% rel. intensity, ion): 226 (23, M^+), 225[35, (M^+–H)], 211 [12, M^+–Me)], 135 [100, (M^+–Tol)], 119 [5, M^+–Ans)], 92 (29), 77 (18).

(4-Methoxyphenyl)(2,6-dimethylphenyl)methanone (3bd).[22] MS (EI, 70eV) *m/z* (% rel. intensity, ion): 240 (34, M^+), 239 [46, (M^+–H)], 225 [24, (M^+–Me)], 209 [100, (M^+–OMe)], 135 (77), 105 (30), 92 (47), 77 (91).

(3,5-Dimethoxyphenyl)(2,6-dimethylphenyl)methanone (3dd). Yellowish solid: mp 83-86 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 7.20 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 2H), 6.95 (d, J = 2.3 Hz, 2H), 6.67 (t, J = 2.3 Hz, 1H), 3.80 (s, 6H), 2.13 (s. 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ(ppm) 200.3 (CO), 161.3 (C), 139.7 (C), 139.2 (C), 134.3 (C), 128.9 (CH), 127.7 (CH), 107.2 (CH), 106.1 (CH), 55.7 (CH_3), 19.5 (CH_3); MS (EI, 70eV) *m/z* (% rel. intensity, ion): 270 (100, M^+), 255 [54, (M^+–Me)], 105 (90), 92 (19), 77 (99); Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.66; H, 6.53.

(3,4-dimethoxyphenyl)(2,6-dimethylphenyl)methanone (3ed). White solid: mp 82-84 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 7.61 (d, J = 1.6 Hz, 1H), 7.22 (t, J = 7.7 Hz, 1H), 7.17 (dd, J = 8.4 Hz; J = 1.6 Hz, 1H), 7.07 (d, J = 7.7 Hz, 2H), 6.80 (d, J = 8.4 Hz, 1H) 3.94 (s, 3H), 3.93 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ(ppm) 199.2 (CO), 154.0 (C), 149.6 (C), 140.0 (C), 134.3 (C), 130.6 (C), 128.7 (CH), 127.6 (CH), 125.6 (CH), 110.3 (CH), 110.3 (CH), 56.2 (CH_3), 56.2 (CH_3), 19.5 (CH_3); MS (EI, 70eV) *m/z* (% rel. intensity, ion): 270 (62, M^+), 255 [16, (M^+–Me)], 240 [100, M^+–2Me)], 105 (27), 92 (9), 79 (51); Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.64; H, 6.74.

(3,4,5-Trimethoxyphenyl)(2,6-dimethylphenyl)methanone (3fd). White solid: mp 57-60 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 7.22 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 7.4 Hz, 2H), 7.06 (s, 2H), 3.93 (s, 3H), 3.81 (s, 6H), 2.14 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ(ppm) 199.4 (CO), 153.5 (C), 143.4 (C), 139.6 (C), 134.3 (C), 132.4.9 (C), 128.9 (CH), 127.7 (CH), 107.0 (CH), 66.1 (CH_3), 56.4 (CH_3), 19.5 (CH_3); MS (EI, 70eV) *m/z* (% rel. intensity, ion): 300 (100, M^+), 285 [20, (M^+–Me)], 270 [96, (M^+–2Me)], 225 (21), 133 (32), 105 (60), 92 (7), 77 (58); Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.06; H, 6.84.

Computational Procedure

The calculations were performed with Gaussian09.[25] 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 chlorides and their radical anions. Zero point energy and thermal energy were computed at the 6-31+G* level and scaled by a factor 0.986[26] for adiabatic EAs and thermodynamic quantities. The potential energy surface was inspected through a scan of the distinguished reaction coordinate. That is, by elongating the C(O)-Cl bond (steps of 0.01 Å each) at B3LYP/6-31+G* level with full optimization for the remainder degrees of freedom. The energy profile obtained is shown in Figure 3. 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 QST2 methodology for a transition state. All calculations were performed in gas phase.[27]

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Notes and references

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† Electronic Supplementary Information (ESI) available: *xyz* coordinates and total energies in atomic units for all of the calculated structures and copy of ^{1}H and ^{13}C NMR spectra of unknown compounds **3ed**, **3dd** and **3fd**. See DOI: 10.1039/b000000x/

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