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One-Step Conversion of Methyl Ketones to Acyl Chlorides

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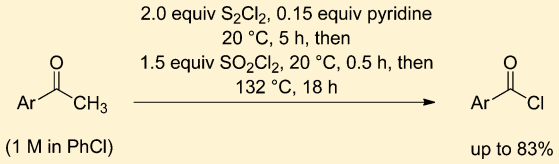
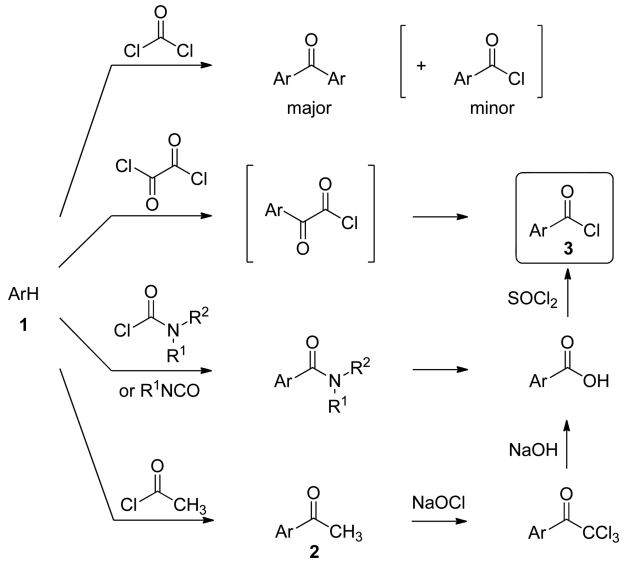
Supporting Information

ABSTRACT: Treatment of aromatic and heteroaromatic methyl ketones with sulfur monochloride and catalytic amounts of pyridine in refluxing chlorobenzene leads to the formation of acyl chlorides. Both electron-rich and electron-poor aryl methyl ketones can be used as starting materials. The resulting C_1-byproduct depends on the precise reaction conditions chosen.



The direct chlorocarbonylation of arenes or heteroarenes with phosgene hardly ever gives high yields of aroyl chlorides, giving symmetric ketones instead. Therefore, a number of alternative reagents have been identified (chlorosulfonyl isocyanate,[1] other sulfonyl isocyanates,[2] other isocyanates,[3] carbamyl chlorides,[4] carbamates,[5] and ureas[6]) that enable the conversion of arenes to arenecarboxylic acid amides. The latter, however, must be hydrolyzed to carboxylic acids to be converted to acyl chlorides. Only oxalyl chloride enables direct one-step chlorocarbonylation of arenes,[7] but unfortunately, it is rather expensive (Scheme 1).

Scheme 1. Strategies for the Preparation of Aroyl Chlorides 3 from Arenes 1



Another strategy for the conversion of arenes or heteroarenes **1** to aroyl chlorides **3** is Friedel–Crafts acetylation followed by haloform reaction to obtain the carboxylic acids and, finally, treatment with thionyl chloride (last equation, Scheme 1). Disadvantages of this multistep methodology are the high dilution of the haloform reaction, the formation of hypochlorous acid and chlorine during acidification of aqueous hypochlorite, which can cause the formation of chlorinated byproducts,[8] and the large number of manipulations, all of which make this strategy costly and inefficient.

The use of methyl ketones **2** as intermediates could, however, become economically attractive if a low-cost, one-step conversion of methyl ketones to acyl chlorides were to become available. To my knowledge, no high-yield, one-step conversion of methyl ketones to acyl chlorides has been reported to date. Some results in the literature suggested, however, that such a reaction may be possible. For instance, treatment of acetophenone or pinacolone with ten equiv of thionyl chloride in the presence of a catalytic amount of pyridine, followed by distillation, gave low yields of the corresponding acyl chlorides (Scheme 2).[9,10]

Reaction of Aromatic Methyl Ketones with Thionyl Chloride. The yield of the reaction in Scheme 2 could be improved by treating methyl ketones **2** with 4–6 equiv of thionyl chloride first at 60–75 °C for some hours, and then at 140 °C for 15–20 h, while allowing volatiles to evaporate off (Scheme 3). The only C_1-byproduct we were able to detect (by GC-MS and ^{13}C NMR) was trichloromethanesulfenyl chloride.

Analysis of the reaction mixture by ^1H and ^{13}C NMR suggested that intermediate **4a** was not a precursor of benzoyl chloride but had to be oxidized further to intermediates **6a**. Variable amounts of trichloromethyl ketones were also formed and were the most unreactive intermediates **6a**. These trichloromethyl ketones, however, were also converted to aroyl chlorides if enough thionyl chloride had been used and if the reaction at 140 °C was allowed to proceed for enough time. Because we were unable to convert isolated, aromatic trichloromethyl ketones into aroyl chlorides with a variety of reagents, I assume that this conversion was mediated by some decomposition product of thionyl chloride.

The protocol with thionyl chloride had several disadvantages. If less than 4–6 equiv of thionyl chloride was used, the reaction mixture solidified and only low yields of acyl chlorides resulted. If solvents were used (e.g., chlorobenzene), the reaction slowed

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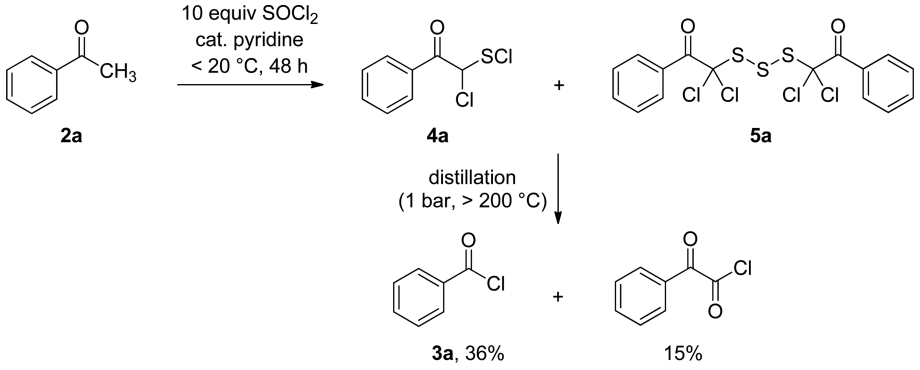
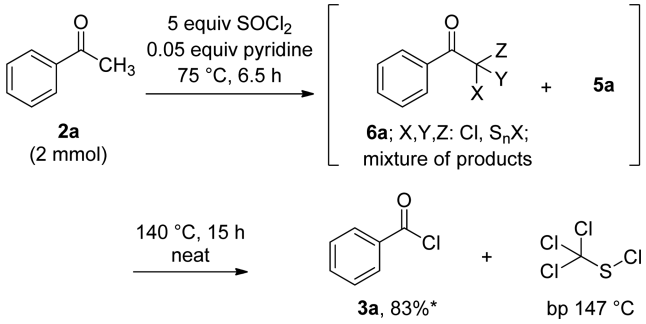
Scheme 2. Reaction of Acetophenone with Thionyl Chloride[9,10]



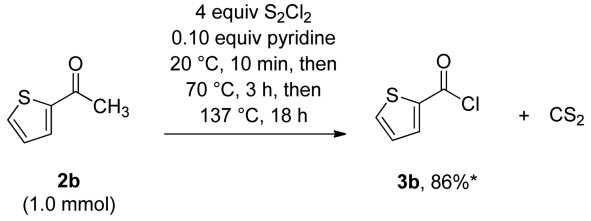
Scheme 3. Optimized Reaction Conditions for the Conversion of Acetophenone to Benzoyl Chloride with Thionyl Chloride*



*Yield determined by ^{1}H NMR of the crude product mixture with an internal standard.

When aromatic methyl ketones were treated with S_2Cl_2 under conditions similar to those used with $SOCl_2$, clean formation of acyl chlorides was observed (Scheme 4).

Scheme 4. Reaction of 2-Acetylthiophene with Sulfur Monochloride*



*Yield determined by ^{1}H NMR of crude product mixture with an internal standard.

dramatically, and no complete conversion to the acyl chlorides could be attained. With electron-rich methyl ketones (e.g., 2-acetylthiophene), large amounts of dark, insoluble material were formed, and the yields of the crude electron-rich aroyl chlorides never exceeded 70%. Moreover, the desired aroyl chlorides were often contaminated with substantial amounts of trichloromethyl ketones, and it was unclear which parameters of the reaction were causing their formation. When the first step in Scheme 3 was run at lower temperatures with a large excess of thionyl chloride, the amount of trichloromethyl ketones decreased. Such a protocol, however, was too expensive because of the high dilution and large excess of thionyl chloride. For these reasons, an alternative to the thionyl chloride method was sought.

Reaction of Aromatic Methyl Ketones with Sulfur Monochloride. Adiwidjaja et al. had mentioned[10] that "yellow, commercial thionyl chloride" was better suited for reactions with ketones than freshly distilled thionyl chloride. One of the known decomposition products of thionyl chloride is sulfur monochloride[11] (S_2Cl_2, bp 137 °C). It was also known that less highly oxidized sulfur chlorides (e.g., sulfenyl chlorides, RSCl) are stronger sulfenylating and weaker chlorinating reagents than more strongly oxidized sulfur chlorides (e.g., thionyl chloride or sulfuryl chloride). Because one problem of the thionyl chloride reaction was the formation of trichloromethyl ketones, it was decided that the reaction of sulfur monochloride with ketones should be investigated with the hope that perchlorination of the ketone would be less extensive with this reagent.[12]

When compared to the reactions with thionyl chloride, sulfur monochloride provided higher yields of acyl chlorides, especially in the case of electron-rich methyl ketones. Under optimal conditions, the amount of trichloromethyl ketones remained below 10%. The darkening of the reaction mixture was less intense than with thionyl chloride, and the scope of suitable starting materials was broader. Thus, acetophenones substituted with methoxy, fluorine, trifluoromethyl, nitro, or phenyl groups, and even 2-acetylfuran, yielded the expected acyl chlorides under the conditions given in Scheme 4.

Analysis of the volatile components formed during the reaction of methyl ketones with S_2Cl_2 revealed that large amounts of carbon disulfide (CS_2) were being formed as C_1-byproduct. Because of the high flammability of CS_2, such a reaction was deemed too dangerous for large scale preparations. To minimize this problem, a new protocol was developed in which sulfuryl chloride was added to the reaction mixture after the initial reaction of the ketone with S_2Cl_2 in order to chlorinate any precursor of CS_2 or any CS_2 to Cl_3CSCl, S_2Cl_2, or CCl_4.[13]

Reaction of Aromatic Methyl Ketones with Sulfur Monochloride and Sulfuryl Chloride. Addition of sulfuryl chloride (or thionyl chloride) to the reaction mixture after the initial step of the reaction of methyl ketones with S_2Cl_2 had occurred provided for a cleaner reaction and enabled the use of chlorobenzene as solvent (Scheme 5, Table 1). The use of a solvent was beneficial because the reactions without solvent (Scheme 4) often became viscous and difficult to stir, particularly if only three equiv of S_2Cl_2 had been used.

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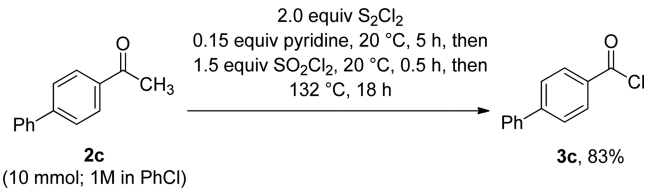
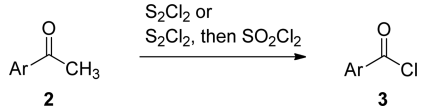
Scheme 5. Optimized Conversion of Methyl Ketones into Acyl Chlorides with S_2Cl_2/SO_2Cl_2



2c (10 mmol; 1M in PhCl) **3c**, 83%

Table 1. Yields of Crude and Isolated Acyl Chlorides 3 Obtained with S_2Cl_2 Alone or with S_2Cl_2/SO_2Cl_2



2 **3**

		S_2Cl_2 alone[a]		S_2Cl_2 and SO_2Cl_2[b]	
ArAc	Ar	equiv S_2Cl_2	crude	crude	isolated
2a	phenyl	4.0	82%	87%	*c*
2b	2-thienyl	4.0	86%	90%	*c*
2c	4-biphenylyl	3.5	83% (68%)[d]	90%	83%
2d	4-nitrophenyl	3.5	83%	90%	71%[e]
2e	2-naphthyl	3.5	82%	91%	69%
2f	4-methoxyphenyl	3.0	91%	86%	63%
2g	3,4-dimethoxyphenyl	4.0	79%	77%	47%
2h	2-furyl	3.5	44%	65%	
2i	5-chloro-2-thienyl	3.0	68%	80%	

[a]The ketone was mixed with S_2Cl_2 and pyridine (0.15 equiv) and stirred first at 75 °C for 2.5 h and then at 137 °C for 19 h. [b]The ketone, pyridine (0.15 equiv), chlorobenzene, and S_2Cl_2 (2.0 equiv) were stirred at 20 °C for 2–6 h. Then, SO_2Cl_2 (1.5 equiv) was added, and the mixture was stirred at 20 °C for 0.5 h and then at 132 °C for 15–20 h. [c]The purity of the distilled products (20 cm Vigreux column, 100 mmol scale) was 70–80%. [d]Isolated yield in parentheses. [e]S_2Cl_2 (1.5 equiv) and SO_2Cl_2 (2.0 equiv) were used.

When the amount of product was determined by ^{1}H NMR of the reaction mixture with an internal standard, yields were generally 80–90%, and no starting material or intermediates could be detected. Purification of the acyl chlorides was best accomplished by evaporation of the solvent, dilution of the residue with hexane, decantation, and crystallization at low temperature or careful distillation. Complete removal of sulfur and sulfur chlorides, however, proved difficult. Most solvents suitable for recrystallizing acyl chlorides also dissolve sulfur and its chlorides, and a single recrystallization was rarely enough to obtain products with >90% purities.

When applying the conditions of Scheme 5 to 4-nitroacetophenone **2d**, partial (<5%) reduction of the nitro group occurred. This could be prevented by using 1.5 equiv of S_2Cl_2 and 2.0 equiv of SO_2Cl_2.

Because of their high reactivity, acyl chlorides are usually not purified but rather are used as crude products directly after their preparation. After evaporation of chlorobenzene and sulfur monochloride, the main nonvolatile byproduct of the current preparation is sulfur, which should not interfere in most reactions of acyl chlorides.

Although no detailed mechanistic studies of this new reaction have been performed, various results from the literature and my own observations point toward a mechanism as sketched in Scheme 6.

As reported,[14] the reaction of C–H acidic compounds with sulfur chlorides can lead to thiolation or chlorination at carbon. It is also known[15] that (chloroacetyl)arenes react with sulfur to yield α-oxodithiocarboxylic acids **8**. The formation of carbon disulfide as a C_1-byproduct indicates that α-oxodithiocarboxylic acids **8** could indeed be intermediates of the present reaction.

Because chloride is a poor nucleophile and almost no chlorine-mediated C–C bond cleaving reactions are known, an intramolecular transfer of chloride to the carbonyl C atom seems likely. The precursor of the acyl chloride could be an *S*-chloro α-oxodithiocarboxylate **9**, or compounds such as $ArCOC(=S)(S)_nCl$, but this remains to be proven.

Sulfuryl chloride appears to facilitate the formation of acyl chlorides (Scheme 5). This may be caused by further activation of the *S*-chloro α-oxodithiocarboxylate **9**, by chlorination for instance, to yield compounds such as **10**. Thioketones, for instance, undergo facile chlorination to yield α-chlorosulfenyl chlorides.[16]

If the mechanism in Scheme 6 is correct, sulfuryl chloride should be replacable by chlorine, which would reduce the amount of waste generated by this process and its overall costs even further. For laboratory preparations, however, sulfuryl chloride is easier to dose and handle than chlorine.

EXPERIMENTAL SECTION

Chemical shifts (δ) in NMR spectra are reported in ppm relative to Me_4Si (δ = 0.00 ppm). All reagents and starting materials were commercially available and used without further purification. Reactions on a 1–2 mmol scale were performed by mixing all reagents and starting materials at once, followed by heating. Addition of an internal standard (iBu_3PO_4), dilution with $CDCl_3$, filtration, and analysis by ^{1}H NMR gave an estimate of the yield and purity of the acyl chlorides (Table 1). Larger scale reactions had to be conducted in a dosage-controlled manner to prevent thermal runaway. In the present case, the most convenient procedure was to add 1/10th to 1/5th of a solution of the starting ketone and the catalyst (pyridine or 3-picoline) in a minimal amount of chlorobenzene to sulfur monochloride and heat the mixture until HCl evolution started. The remainder of the ketone solution was then added at room temperature to the cooled reaction mixture at such a rate that the reaction remained controllable. Addition funnels tended to get clogged because the evolving HCl caused pyridine hydrochloride to precipitate from the ketone solution.

All products were known, commerically available compounds and identified by comparison of their ^{1}H and ^{13}C spectra with the reported spectra. Because the typical impurities (S_8, S_6, Cl_3CSCl, S_2Cl_2) were difficult to detect and quantify, the purity of the products was determined by ^{1}H NMR weight % determination with an internal standard (triisobutyl phosphate).

Typical Procedure for the Synthesis of Acyl Chlorides 3 from Methyl Ketones 2 with Sulfur Monochloride Alone: 4-Phenylbenzoyl Chloride. To sulfur monochloride (4.80 mL, 60.0 mmol) at room temperature were added 4-phenylacetophenone (716 mg, 3.31 mmol) and pyridine (0.081 mL, 1.00 mmol), and the mixture was heated to 80–90 °C for approximately 10 min, when strong HCl formation set in. The mixture was cooled to room temperature with a water bath, and the remainder of 4-phenylacetophenone (total: 3.85 g, 19.6 mmol) and pyridine (total: 0.32 mL, 4.0 mmol) was added in three portions within 20 min. The mixture became increasingly viscous and difficult to stir. After 1 h at room temperature, the mixture was heated to 140 °C (oil bath temperature) and stirred at this temperature for 16 h. The mixture was allowed to cool, and the product was extracted two times by adding hexane (50 mL), heating to reflux, and decanting. The combined hexane phases were kept at −30 °C for 3 h and decanted, and the solid was recrystallized once more from hexane (150 mL). 4-Phenylbenzoyl chloride (3.06 g, 95% pure, yield: 68%) was obtained as yellow needles.

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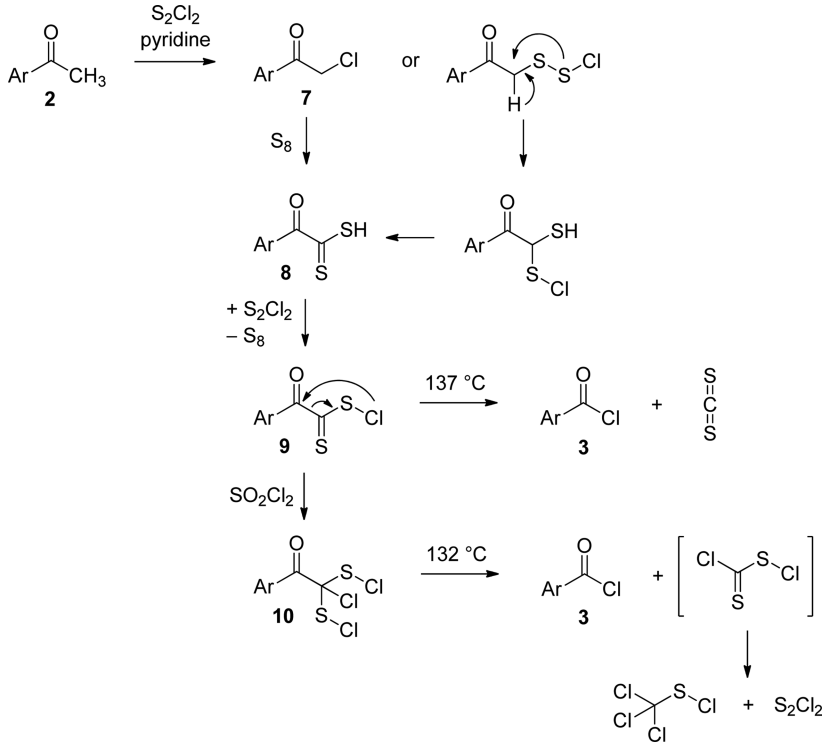
Scheme 6. Possible Mechanism of the Formation of Acyl Chlorides 3 from Methyl Ketones 2, Sulfur Monochloride, and Sulfuryl Chloride



General Procedure for the Synthesis of Acyl Chlorides 3 from Methyl Ketones 2 with Sulfur Monochloride and Sulfuryl Chloride. To sulfur monochloride (1.6 mL, 20 mmol) at room temperature was added 1/5th of a solution of methyl ketone **2** (10.0 mmol) and pyridine (0.121 mL, 1.50 mmol) in chlorobenzene (3.5 mL or the minimal amount required to dissolve the ketone upon slight heating). The mixture was heated for 5−20 min to ∼80 °C until steady HCl evolution set in. The mixture was then cooled to room temperature with a water bath, and the remainder of the ketone solution was added to the stirred reaction mixture at such a rate that HCl formation did not become too violent (usually 15−30 min). The mixture was stirred at room temperature for 2−6 h. Sulfuryl chloride (1.21 mL, 15.0 mmol) was then added dropwise within 20 min (strong gas evolution, no strong exotherm). The resulting mixture was stirred at room temperature for 0.5 h and then at slight reflux (oil bath: 137 °C) for 15−20 h.

Chlorobenzene and sulfur chloride were evaporated (40 mbar, 120 °C), and the residue was diluted with hexane (50 mL). The mixture was stirred at room temperature, whereupon a clear solution and a dark, oily precipitate resulted. The solution was decanted off the dark oil or filtered, the flask was rinsed with hexane (5 mL), and the combined hexane phases were allowed to crystallize at 5 to −30 °C. Inverse filtration, washing with cold hexane, and drying under reduced pressure yielded the acyl chlorides (**3**). Repeated recrystallization or distillation was often required to remove residual sulfur, sulfur chlorides, and Cl_3CSCl.

*4-Phenylbenzoyl Chloride (**3c**, CAS Registry 14002-51-8).* Following the general procedure, using 10 mL of chlorobenzene yielded the product in two crops (1.59 g, purity: 96%, yield: 70%; and 0.32 g, purity: 92%, yield: 13%; total yield: 83%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (m, 2H), 7.71 (m, 2H), 7.62 (m, 2H), 7.50−7.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.1, 148.1, 139.1, 132.1, 131.9, 129.1, 128.9, 127.5, 127.4.

*4-Nitrobenzoyl Chloride (**3d**, CAS Registry 122-04-3).* Following the general procedure, using 5 mL of chlorobenzene, 1.20 mL (15 mmol) of S_2Cl_2, and 1.62 mL (2.0 mmol) SO_2Cl_2 yielded the product in two crops (882 mg, purity 93%, yield: 44%; and 545 mg, purity: 91%, yield: 27%; total yield: 71%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40−8.36 (m, 2H), 8.34−8.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 151.6, 138.0, 132.2, 124.0.

*Naphthalene-2-carbonyl Chloride (**3e**, CAS Registry 2243-83-6).* Following the general procedure on a 15 mmol scale, using 5 mL of chlorobenzene yielded, after a single crystallization from hexane (70 mL) at −30 °C, 2.17 g (69% yield) of the product with a purity of 90%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.68 (s, 1H), 8.00 (dd, J = 8 Hz, 1 Hz, 1H), 7.95 (d, J = 8 Hz, 1H), 7.86 (m, 2H), 7.65 (m, 1H), 7.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4, 136.4, 134.8, 132.3, 130.4, 130.0, 129.9, 128.8, 127.9, 127.4, 125.3.

*4-Methoxybenzoyl Chloride (**3f**, CAS Registry 100-07-2).* Following the general procedure on a 20 mmol scale, using 7 mL of chlorobenzene yielded, after a single crystallization from hexane (30 mL) at −30 °C, 2.42 g (63% yield) of the product with a purity of 89%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, J = 8 Hz, 2H), 6.96 (d, J = 8 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 165.4, 134.0, 125.5, 114.3, 55.8.

*3,4-Dimethoxybenzoyl Chloride (**3g**, CAS Registry 3535-37-3).* Following the general procedure on a 15 mmol scale, using 5 mL of chlorobenzene yielded, after a single crystallization from hexane (60 mL) at −30 °C, 1.52 g (47% yield) of the product with a purity of 92%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (dd, J = 8 Hz, 1 Hz, 1H), 7.53 (d, J = 1 Hz, 1H), 6.94 (d, J = 8 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.2, 155.2, 149.0, 127.2, 125.5, 112.8, 110.4, 56.3, 56.1.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01707.

Copies of ^{1}H and ^{13}C NMR spectra of the isolated acyl chlorides **3c**−**3g** (PDF)

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Notes

The authors declare no competing financial interest.

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