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# Highly selective catalytic Friedel–Crafts acylation and sulfonylation of activated aromatic compounds using indium metal

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**Abstract**—The Friedel–Crafts acylation of activated benzenes with various aromatic and aliphatic acid chlorides was studied in the presence of indium metal. The reaction was accomplished in high isolated yields under solvent or solvent-less conditions. The method is also applicable for preparing diaryl sulfones from aromatic compounds and aryl sulfonyl chlorides.

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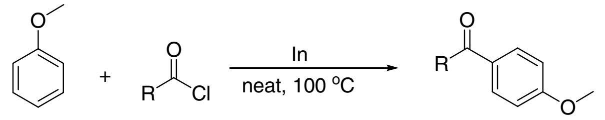
Aromatic ketones are important intermediates for preparing fine chemicals in the field of pharmaceuticals, fragrances, and agrochemicals. Aromatic ketones have been prepared conventionally by Friedel–Crafts acylation of aromatic compounds with acid chlorides using more than stoichiometric amounts of anhydrous strong Lewis acids such as $AlCl_3$, $TiCl_3$, $FeCl_3$, or $SnCl_4$.[1] However, these Lewis acids are very sensitive to moisture. Hence moisture-free reaction conditions are required to attain the optimal yields of the desired products. Moreover, the Friedel–Crafts acylations based on the use of above mentioned Lewis acids have other problems including high toxicity, corrosion, generation of a large amount of waste, and difficulty in purifying the desired products. Thus, the need for developing Friedel–Crafts acylation of aromatic compounds with moisture insensitive catalysts remains strong. Varieties of catalysts for Friedel–Crafts acylation of aromatic compounds have been reported.[2]

In recent years, indium-mediated reactions have received considerable attention owing to the unique properties of indium metal.[3] Indium metal is stable in air or in oxygen at ambient temperature, and it is practically inert even in boiling water. In addition, its toxicity is low. These special properties inherent to indium metal prompted us to apply it in organic synthesis.[4] Herein we report a method of Friedel–Crafts acylation and sulfonylation of aromatic compounds in the presence of indium metal.

The activity of indium metal as a promoter of Friedel–Crafts acylation of anisole with various acid chlorides was examined (Table 1). Anisole was allowed to react

**Table 1.** The Friedel–Crafts acylation of anisole under various reaction conditions



| Entry | R | In (equiv) | Time (h) | Isolated yield (%)[a] |
|---|---|---|---|---|
| 1 | Cyclohexyl | 1 | 4 | 98 |
| 2 | Cyclohexyl | 0 | 4 | 0 |
| 3 | Adamantyl | 1 | 4 | 70 |
| 4 | $C_6H_5$ | 1 | 2 | 76 |
| 5 | $p$-$NO_2$–$C_6H_4$ | 1 | 2.5 | 78 |
| 6 | $^t$Butyl | 1 | 6 | 76 |
| 7 | $^t$Butyl | 3 | 2 | 78 |
| 8 | $^t$Butyl | 1 | 4 | 80[b] |
| 9 | $C_6H_5$ | 0.2 | 2 | 83 |

[a] The reaction was carried out under the conditions of 1:6 molar ratio of acid chlorides and anisole, and the yield was calculated based on acid chlorides.

[b] The reaction was carried out in dioxane.

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*Keywords*: Friedel–Crafts acylation; Sulfonylation; Indium; Aromatic ketones; Acid chlorides.

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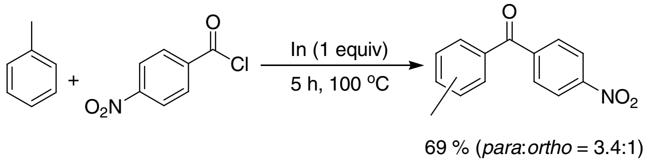
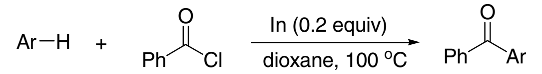
with cyclohexanecarbonyl chloride in the presence of indium metal in boiling dioxane for 4 h affording the acylated product in 98% yield (entry 1). The same reaction without indium metal did not proceed, implying that indium metal is the active promoter in the reaction (entry 2). 1-Adamantanecarbonyl chloride, benzoyl chloride, and *p*-nitro benzoyl chloride were good substrates for the present process (entries 3–5). The reaction proceeded efficiently even with highly sterically hindered pivalolyl chloride affording high yields of the acylated product (entry 6). An increase in the amount of indium was found to shorten the reaction time (entry 6 vs 7). The reaction was accomplished in dioxane without detrimental effects on the yield of the product (entry 8). We also found it possible to accomplish the reaction with a catalytic amount of indium metal. The reaction of anisole with benzoyl chloride with 0.2 equiv of indium metal produced the corresponding aryl ketone without affecting the yield of the product (entry 9). The Friedel–Crafts acylation of anisole under the present reaction conditions produced a *para* isomer as the sole product with no detection of *ortho* and/or *meta* isomers, indicating a high selectivity in the acylation of anisole. However, when toluene was allowed to react with *p*-nitrobenzoyl chloride under the reaction conditions, the corresponding aromatic ketones were produced in 69% yield with an *ortho*:*para* ratio of 3.4:1 (Scheme 1).



**Scheme 1.**

The benzoylations of various aromatic compounds were attempted in the presence of a catalytic amount of indium metal to examine the scope and limitations of the reaction. The results are summarized in Table 2. The indium-mediated benzoylations of benzene with electron-donating groups such as *N*,*N*-dimethylaniline, 1,3,5-trimethoxybenzene, 1,4-dimethoxybenzene, and thioanisole gave high yields of the corresponding aryl ketones with a catalytic amount of indium metal in boiling dioxane (entries 1–4). In the case of alkyl benzenes such as toluene and xylene, the benzene ring is less activated; hence it is more difficult to accomplish the acylation of alkyl benzenes (entries 5 and 6). With mesitylene, the yield of the product was 58% at 100 °C and 77% at 150 °C (entries 7 and 8). Deactivated benzenes such as chlorobenzene and bromobenzene were inactive under the reaction conditions (entries 9 and 10). These results show that the indium-mediated Friedel–Crafts acylation is favored by the presence of electron-donating groups such as alkyl, alkoxy, or alkyl amine in the aromatic compounds whereas it is inhibited by the presence of electron withdrawing groups such as halo functionality.

**Table 2.** Indium-mediated Friedel–Crafts acylation of various aromatic compounds with benzoyl chloride



| Entry | Ar–H | Time (h) | Isolated yield (%)[a] |
|---|---|---|---|
| 1 | *N*,*N*-Dimethylaniline | 0.75 | 92 |
| 2 | 1,3,5-Trimethoxybenzene | 1.5 | 91 |
| 3 | 1,4-Dimethoxybenzene | 2 | 87 |
| 4 | Thioanisole | 2 | 90 |
| 5 | Toluene | 2.5 | 21[c] |
| 6 | *p*-Xylene | 2.5 | 40[c] |
| 7 | Mesitylene | 1.5 | 60[c] |
| 8 | Mesitylene | 0.5 | 77[b,c] |
| 9 | Chlorobenzene | 5 | 0[c] |
| 10 | Bromobenzene | 5 | 0[c] |

[a] The reaction was carried out under the conditions of 1:6 molar ratio of benzoyl chloride and aromatic compounds, and the yield was calculated based on benzoyl chloride.

[b] The reaction was carried out at 150 °C.

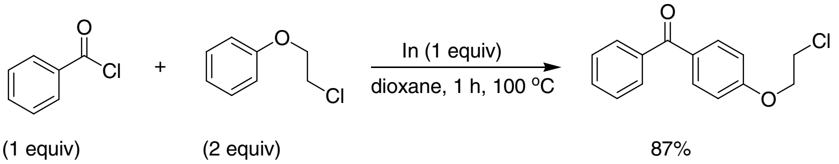
[c] The reaction was performed with 1 equiv of indium under solvent-less conditions.

We carried out a competitive experiment to study the selectivity of the reaction. A mixture of toluene and anisole with a ratio of 1:1 was allowed to react with benzoyl chloride in the presence of indium metal at 100 °C for 1 h, and the products were analyzed. Since 4-methoxyacetophenone was obtained as a sole product in 81% yield, a high selectivity was found between alkoxy and alkyl groups on the benzene ring.

The present reaction was applied to the preparation of an intermediate for the synthesis of a tamoxifen derivative which is a good candidate for the treatment of estrogen-dependent breast tumors (Scheme 2).[5] When the reaction mixture of benzoyl chloride (1 equiv), 2-chloroethoxybenzene (2 equiv) and In (1 equiv) in dioxane was stirred at 100 °C for 1 h, the desired product, 4-(2-chloroethoxy)benzophenone, was obtained in 87% isolated yield.

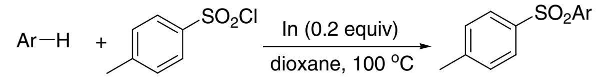
Next, we utilized our method in preparing diaryl sulfones, which are important intermediates for synthesizing medicines.[6] Conventionally, diaryl sulfones are prepared using strong Lewis acids.[1a] A variety of activated aromatic compounds were transformed into the corresponding diaryl sulfones in excellent yields under the present reaction conditions. The results are summarized in Table 3. The reaction of activated benzenes with *p*-toluenesulfonyl chloride in the presence of a catalytic amount of indium metal furnished the corresponding diaryl sulfones in high yields (entries 1–5). With moderately activated alkyl benzenes such as xylenes, low yields were obtained (entries 6 and 7). In the case of mesitylene, the corresponding diaryl sulfone was obtained in 82% yield (entry 9).

It was observed that the presence of a radical scavenger such as BHT (butylated hydroxytoluene) and TEMPO (2,2,6,6-tetramethylpiperidine oxide) showed no effects on the reaction in terms of the reaction rate and the yield of the product. This implied that the reaction did not proceed via a radical pathway. We also observed a



**Scheme 2.**

**Table 3.** Indium-mediated sulfonylation of various aromatic compounds with *p*-toluenesulfonyl chloride



| Entry | Ar–H | Time (h) | Isolated Yield (%)[a] |
|---|---|---|---|
| 1 | Anisole | 2 | 76 |
| 2 | *N*,*N*-Dimethylaniline | 1.5 | 84 |
| 3 | 1,3,5-Trimethoxybenzene | 3 | 71 |
| 4 | 1,4-Dimethoxybenzene | 2 | 77 |
| 5 | Thioanisole | 2 | 82 |
| 6 | *p*-Xylene | 2 | 23[b] |
| 7 | *m*-Xylene | 1 | 40[b] |
| 8 | Mesitylene | 1.5 | 82[b] |

[a] The reaction was carried out under the conditions of 1:6 molar ratio of *p*-toluenesulfonyl chloride and aromatic compounds, and the yield was calculated based on *p*-toluenesulfonyl chloride.

[b] The reaction was performed with 1 equiv of indium under solvent-less conditions.

metallic shiny species during the reaction, which might be the regenerated indium. At present, although the possibility of the participation of indium chloride generated in situ as a promoter for the reaction cannot be excluded,[7] we suggest that the reaction is likely to proceed by an ionic pathway involving an indium complex having an alkyl or aryloxocarbenium ion character,[8] which reacts with aromatic compounds to generate the Friedel–Crafts acylation product and indium metal along with HCl.

In conclusion, we developed a method of synthesizing aryl ketones and diaryl sulfones by means of indium-mediated Friedel–Crafts acylation and sulfonylation of aromatic compounds, which showed a good selectivity for the activated aromatic compounds. The present process is not only easy to perform but also has other advantages such as low toxicity and no pretreatment of the reagents.

A typical experimental procedure is as follows: Anisole (0.48 mL, 4.42 mmol), benzoyl chloride (84 μL, 0.73 mmol), indium powder (16.8 mg, 0.15 mmol) and dioxane (0.5 mL) were placed in a two-necked flask, and the resulting mixture was stirred at 100 °C for 2 h under nitrogen. The mixture was then quenched with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and purified by column chromatography on silica gel, eluting with hexane: EtOAc (20:1) to give the corresponding aryl ketone (129 mg, 83%).

## Acknowledgements

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## References and notes

1. (a) Olah, G. A. In *Friedel–Crafts and Related Reactions*; Wiley-Interscience: New York, 1964; Vol. III; (b) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley-Interscience: London, 1973; (c) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 733–752.
2. (a) Strekowski, L.; Wydra, R. L.; Cegla, M. T.; Czarny, A.; Patterson, S. *J. Org. Chem.* **1989**, *54*, 6120; (b) Gatti, N. *Tetrahedron Lett.* **1990**, *31*, 3933; (c) Harada, T.; Ohno, T.; Kobayashi, S.; Mukaiyama, T. *Synthesis* **1991**, 1216; (d) Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545; (e) Pivsa-Art, S.; Okura, K.; Miura, M.; Murata, S.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1703; (f) Kawada, A.; Mitamura, S.; Kobayashi, S. *J. Chem. Soc., Chem. Commun.* **1996**, 183; (g) Effenberger, F.; Eberhard, J. K.; Maier, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 12572; (h) Desmurs, J. R.; Labrouillere, M.; Roux, C. L.; Gaspard, H.; Laporterie, A.; Dubac, J. *Tetrahedron Lett.* **1997**, *38*, 8871; (i) Kodomari, M.; Suzuki, Y.; Yoshida, K. *J. Chem. Soc., Chem. Commun.* **1997**, 1567; (j) Nishikido, J.; Nakajima, H.; Saeki, T.; Ishii, A.; Mikami, K. *Synlett* **1998**, 1347; (k) Répichet, S.; Roux, C. L.; Dubac, J.; Desmurs, J. R. *Eur. J. Org. Chem.* **1998**, 2743; (l) Kobayashi, S.; Iwamoto, S. *Tetrahedron Lett.* **1998**, *39*, 4697; (m) Nakano, H.; Kitazume, T. *Green Chem.* **1999**, 179; (n) Matsuo, J.; Odashima, K.; Kobayashi, S. *Synlett* **2000**, 403; (o) Chapman, C. J.; Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Tetrahedron Lett.* **2001**, *42*, 773; (p) Barrett, A. G. M.; Bouloc, N.; Braddock, D. C.; Chadwick, D.; Hendersona, D. A. *Synlett* **2002**, 1653; (q) Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett.* **2002**, *43*, 6331; (r) Choudhary, V. R.; Jana, S. K.; Patil, N. S. *Tetrahedron Lett.* **2002**, *43*, 1105; (s) Répichet, S.; Roux, C. L.; Roques, N.; Dubac, J. *Tetrahedron Lett.* **2003**, *44*, 2307; (t) Gmouth, S.; Yang, H.; Vaultier, M. *Org. Lett.* **2003**, *5*, 2219; (u) Matsushita, Y.-I.; Sugamoto, K.; Matsui, T. *Tetrahedron Lett.* **2004**, *45*, 4723; (v) Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F. *Tetrahedron* **2004**, *60*, 10843; (w) Hosseini, M.; Sharghi, H. *Helv. Chim. Acta* **2005**, *88*, 2282.
3. For reviews: (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023; (b) Lubineau, R.; Angé, J.; Queneau, Y. *Synthesis* **1994**, 741; (c) Cintas, P. *Synlett* **1995**, 1087; (d) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643; (e) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149; (f) Podlech, J.; Maier, T. C. *Synlett* **2003**, 633; (g) Nair, V.; Ros, S.; Jayan, C. N.; Pillia, B. S. *Tetrahedron* **2004**, *60*, 1959.
4. (a) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 631; (b) Cho, D. H.; Kim, J. G.; Jang, D. O. *Bull. Korean Chem. Soc.* **2003**,

*24*, 155; (c) Cho, D. H.; Jang, D. O. *Tetrahedron Lett.* **2004**, *45*, 2285; (d) Munbunjong, W.; Lee, E. H.; Chavasiri, W.; Jang, D. O. *Tetrahedron Lett.* **2005**, *46*, 8769.

5. Coe, P. L.; Scriven, C. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 475.
6. (a) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019; (b) Roy, K. M. In *Ullmann's Encyclopedia of Industrial Chemistry*; Gerhartz, W., Ed.; VCH: Weinham, 1985; Vol. A25, pp 487–501; (c) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, 1993.
7. Although there are some reports on the Friedel–Crafts acylation using indium (III) chloride, the reactions gave very low yields of the products: (a) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Suda, S.; Kobayashi, S. *Chem. Lett.* **1991**, 1059; (b) Chapman, C. J.; Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Tetrahedron Lett.* **2001**, *42*, 773.
8. (a) Alper, H.; Huang, C.-C. *J. Org. Chem.* **1973**, *38*, 64; (b) Inaba, S.-I.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 1373.