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MoO_2Cl_2 as a novel catalyst for Friedel–Crafts acylation and sulfonylation

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ABSTRACT

The use of MoO_2Cl_2 as a novel catalyst for Friedel–Crafts acylation and sulfonylation is described. A series of aromatic ketones and sulfones were prepared in moderate to good yields using acyl chloride or sulfonyl chloride in the presence of MoO_2Cl_2 (20 mol %), under solvent-free conditions.

Friedel–Crafts acylation and sulfonylation provide fundamental and useful methods for the synthesis of aromatic ketones and sulfones, which are important intermediates for preparing fine chemicals in the field of pharmaceuticals, agrochemicals, and fragrances.

Typically, these reactions are performed using acyl chloride (for acylation) or sulfonyl chloride (for sulfonylation) in the presence of a little more than one equivalent of Lewis acids, such as anhydrous $AlCl_3$, $TiCl_4$, and $FeCl_3$. These methods are limited by high amounts, toxicity and corrosion of the catalysts, which are non-recoverable materials after aqueous work-up, generation of a large amount of waste, and difficult purification of the desired products.

Over the last years, a variety of catalysts such as metal halides, zeolites, or mesoporous aluminosilicates have been reported to catalyze Friedel–Crafts acylation and sulfonylation.[1] However, due to the high importance of the Friedel–Crafts reactions in industry, a search for new catalysts is still in demand.

High valent dioxomolybdenum (VI) complexes are known for their abilities to catalyze oxygen-transfer reactions to sulfides, phosphines, and olefins,[2–5] and also as models of molybdoenzymes active sites, such as dimethyl sulfoxide reductases.[6–8]

Recently, we have demonstrated a new reactivity of the high valent oxo-molybdenum complex MoO_2Cl_2 as excellent catalyst for Si–H bond activation and for hydrosilylation of aldehydes and ketones.[9,10] The system silane/MoO_2Cl_2 proved to be also very efficient for the reduction of imines,[11] amides,[12] esters,[13] sulfoxides,[14] and pyridine N-oxides[14] to the corresponding amines, alcohols, sulfides, and pyridines. We also found that MoO_2Cl_2 activates the B–H bond of boranes and catalyzes the reduction of aromatic sulfoxides with boranes in excellent yields.[15]

Other applications of dioxomolybdenum (VI) dichloride complexes as catalysts in organic chemistry include transformation of epoxides to β-alkoxy alcohols, acetonides, and α-alkoxyketones,[16] thioglycosylation of O-acetylated glycosides,[17] thioacetalization of heterocyclic, aromatic, and aliphatic compounds,[18] nucleophilic acyl substitution of anhydrides with a variety of alcohols, amines, and thiols,[19] reductive cyclization of nitro-aromatic compounds,[20] reduction of sulfoxides[21] and pyridine N-oxides.[22]

As part of our continuing studies on the development of new methods catalyzed by high valent oxo-complexes, in this work, we report novel Friedel–Crafts acylation and sulfonylation methods for the synthesis of aromatic ketones and sulfones catalyzed by MoO_2Cl_2.

To optimize the reaction conditions, we first studied the reaction of anisole with *p*-toluoyl chloride catalyzed by MoO_2Cl_2 in different solvents as summarized in Table 1. This reaction was also performed without solvent, using an excess of liquid aromatic compound. The best yields were obtained when the acylation was performed without solvent or in bromobenzene, inert under these conditions (Table 1, entries 1 and 2). The reactions carried out in acetonitrile and dichloromethane gave moderate yields of ketone (Table 1, entries 3 and 4). In THF, a chloroester was isolated as result of THF ring cleavage by reaction with acyl chloride (Table 1, entry 5).[23]

The Friedel–Crafts acylation catalyzed by MoO_2Cl_2 (20 mol %) was explored with a variety of aromatic compounds to evaluate the scope and limitations of this method. The results summarized in Table 2 show that this novel method affords aromatic ketones in

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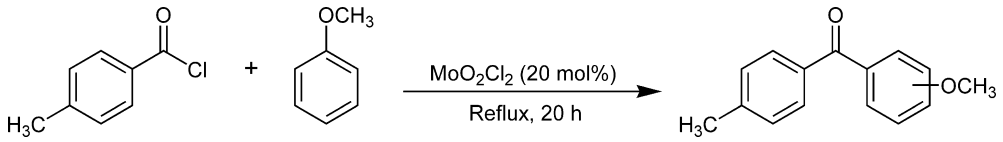
Table 1
Friedel–Crafts acylation of anisole in different solvents[a]



Entry	Solvent	Yield (*para*/*ortho*)[b]
1	Neat	85 (1:0)[c]
2	Bromobenzene	82 (1:0)
3	CH_3CN	62 (20:1)
4	CH_2Cl_2	50 (50:1)
5	THF	Esterification

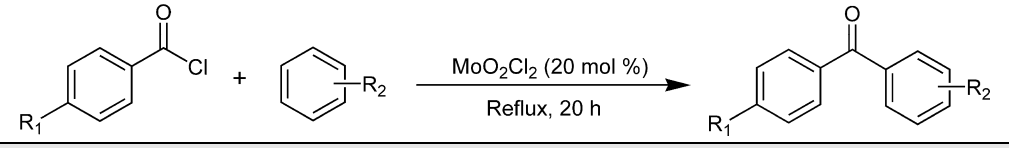
[a] The reactions were carried out with 1 mmol of acyl chloride, 3 mmol of aromatic compound, and 20 mol % of MoO_2Cl_2.
[b] Isolated yields. The ratio of *para*/*ortho*-isomers was determined by ^1H NMR.
[c] The reaction was carried out with 1 mmol of acyl chloride, 30 mmol of aromatic compound, and 20 mol % of MoO_2Cl_2.

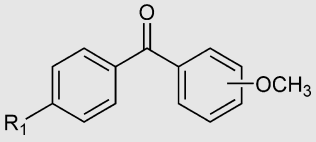
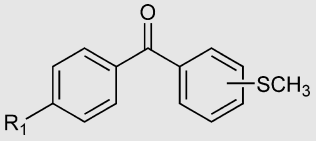
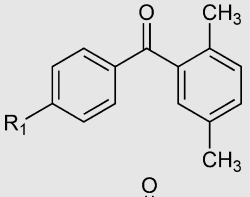
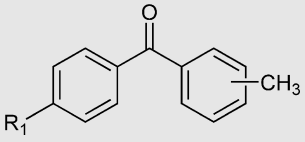
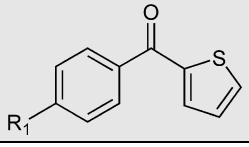
moderate to good yields. The reactions were carried out without solvent, using an excess of liquid aromatic substrates at reflux temperature under inert atmosphere.[24]

The acylation of anisole was investigated with different acyl chlorides. The reaction with 4-chlorobenzoyl chloride produced a mixture of *para*/*ortho*-isomers in 80% yield with a ratio of 17:1 (Table 2, entry 1). Similar acylation with *p*-toluoyl and *p*-anisoyl chlorides afforded exclusively the *para*-isomer in 85 and 81%, respectively (Table 2, entries 2 and 3), indicating a high selectivity with these acyl chlorides. The presence of the strong electron-withdrawing group NO_2 in the acyl chloride reduced drastically the yield of the acylation (34% yield, Table 2, entry 4), and produced a high amount of the corresponding carboxylic acid.

The Friedel–Crafts acylation of thioanisole afforded the aromatic ketones in 56–64% yield. The reaction of thioanisole with

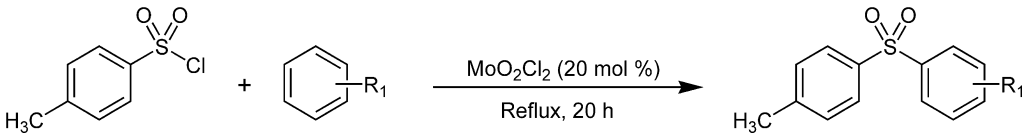
Table 2
Friedel–Crafts acylation catalyzed by MoO_2Cl_2[a]

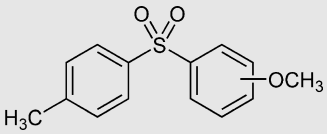
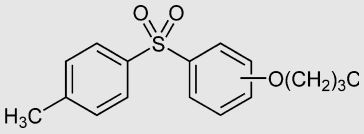
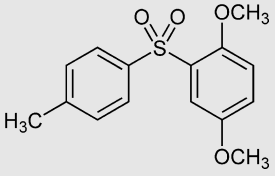
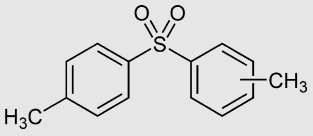
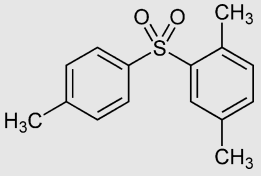
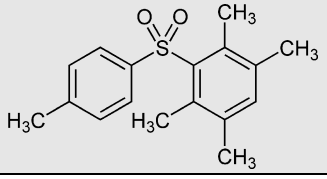


Entry	Acyl chloride	Aromatic compound	Product	Yield[b] (%) (*para*/*ortho*)
1	$R_1 = Cl$	Anisole		80 (17:1)
2	$R_1 = CH_3$	Anisole		85 (1:0)
3	$R_1 = OCH_3$	Anisole		81 (1:0)
4	$R_1 = NO_2$	Anisole		34 (9:1)
5	$R_1 = Cl$	Thioanisole		64 (10:1)
6	$R_1 = CH_3$	Thioanisole		57 (1:0)
7	$R_1 = OCH_3$	Thioanisole		56 (1:0)
8	$R_1 = Cl$	*p*-Xylene		58
9	$R_1 = CH_3$	*p*-Xylene		54
10	$R_1 = OCH_3$	*p*-Xylene		31
11	$R_1 = Cl$	Toluene		54 (4:1)
12	$R_1 = CH_3$	Toluene		50 (13:1)
13	$R_1 = OCH_3$	Toluene		9 (2:1)
14	$R_1 = Cl$	Thiophene		61
15	$R_1 = CH_3$	Thiophene		66
16	$R_1 = OCH_3$	Thiophene		66

[a] All the reactions were carried out with 1 mmol of acyl chloride, 30 mmol of aromatic compound, and 20 mol % of MoO_2Cl_2.
[b] Isolated yields. The ratio of *para*/*ortho*-isomers was determined by ^1H NMR.

Table 3
Friedel–Crafts sulfonylation catalyzed by MoO_2Cl_2[a]



Entry	Aromatic compound	Product	Yield[b] (%) (*para*/*ortho*)
1	Anisole		89 (2:1)
2	*n*-Butyl phenyl ether		66 (8:1)[c]
3	1,4-Dimethoxy-benzene		66[c]
4	Toluene		55 (8:1)
5	*p*-Xylene		44
6	1,2,4,5-Tetra-methylbenzene		45

[a] The reactions were carried out with 1 mmol of sulfonyl chloride, 30 mmol of aromatic compound, and 20 mol % of MoO_2Cl_2.
[b] Isolated yields. The ratio of *para*/*ortho*-isomers was determined by ^1H NMR.
[c] The reaction was carried out with 1 mmol of sulfonyl chloride, 3 mmol of aromatic compound, and 20 mol % of MoO_2Cl_2 in bromobenzene.

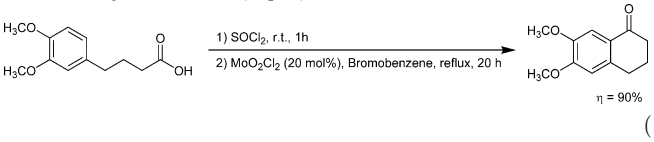
4-chlorobenzoyl chloride gave a mixture of *para*/*ortho*-isomers with a ratio of 10:1 (Table 2, entry 5). In contrast, the reactions with *p*-toluoyl and *p*-anisoyl chlorides were regioselective, yielding only the *para*-isomers (Table 2, entries 6 and 7).

The acylation of alkyl-substituted benzenes such as toluene is more difficult, and some of the methods reported in the literature are not applied to this substrate or gave poor yields of ketone.[1k,n] Under our catalytic conditions, acylation of *p*-xylene gave the corresponding ketones in moderate yields (Table 2, entries 8–10), and the acylation of toluene afforded a mixture of *para*/*ortho*-regioisomers with a high *para*-selectivity (Table 2, entries 11–13). Finally, the deactivated bromobenzene did not react.

The Friedel–Crafts acylation of thiophene with different acyl chlorides was also investigated in the presence of MoO_2Cl_2. These reactions were regioselective, producing only the 2-acyl products in 61–66% yields (Table 2, entries 14–16).

The analysis of the results showed that the best yields were obtained with substrates bearing electron-donating groups, such as alkoxy substituents in the aromatic ring.

Ring closure is another important application of the Friedel–Crafts acylation. The high valent oxo-molybdenum complex MoO_2Cl_2 was successfully applied in the synthesis of 3,4-dimethoxy-α-tetralone by intramolecular Friedel-Crafts acylation with an overall yield of 90% (Eq. 1).



(1)

The reusability of MoO_2Cl_2 was evaluated using anisole as test substrate. We carried out five successive reactions by sequential addition of fresh substrate and *p*-toluoyl chloride to the reaction

mixture. The results obtained showed that the catalytic activity of MoO_2Cl_2 did not decrease with successive uses.

The catalytic activity of MoO_2Cl_2 was also investigated in the sulfonylation of a variety of aromatic compounds with *p*-toluenesulfonyl chloride and methanesulfonyl chloride.[24] Table 3 shows that MoO_2Cl_2 catalyzes the synthesis of aromatic sulfones in moderate to good yields. The reaction of anisole with *p*-toluenesulfonyl chloride afforded a mixture of *para*/*ortho*-isomers (2:1) in 89% yield (Table 3, entry 1). However, similar reaction with methanesulfonyl chloride gave also a mixture of *para*/*ortho*-isomers (1:1) in low yield (4%).

The sulfonylation of *n*-butyl phenyl ether and 1,4-dimethoxybenzene with *p*-toluenesulfonyl chloride was performed in bromobenzene at reflux temperature, and afforded the corresponding sulfones in 66% yield (Table 3, entries 2 and 3).

As shown in Table 3, the alkylbenzenes such as toluene, *p*-xylene and 1,2,4,5-tetramethylbenzene reacted with *p*-toluenesulfonyl chloride, leading to the formation of the corresponding sulfones in 44–55% yields (Table 3, entries 4, 5, and 6).

Mechanistically, we suggest initial activation of the acyl chloride or the sulfonyl chloride by the coordinatively unsaturated and strongly acidic Lewis acid MoO_2Cl_2. This activation can occur by two different addition modes. One possibility involves the carbonyl or sulfonyl group coordination to the molybdenum vacant sites, or MoO_2Cl_2 can also activate the C(O)–Cl or $S(O)_2$–Cl bonds through their addition across Mo=O multiple bond, similar to the activation of anhydrides reported by Chen.[19] In the next step, the complex formed reacts with the aromatic compound, yielding the corresponding acylated product and HCl.

In summary, we developed novel Friedel–Crafts acylation and sulfonylation methods for the synthesis of aromatic ketones and sulfones in moderate to good yields. We also demonstrated that MoO_2Cl_2 catalyzes the formation of C–C and C–S bonds. These results extend the scope of the use of high valent oxo-molybdenum complexes as effective catalysts for organic reactions, and open a new area of catalysis for these complexes, since C–C bond-forming reactions are the essence of organic synthesis.

Further mechanistic studies of these catalytic processes as well as investigations toward the use of oxo-molybdenum complexes in other C–C and C–S bond-forming events are now in progress in our group.

Acknowledgments

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24. In a typical experiment, to a solution of MoO_2Cl_2 (20 mol %) and the aromatic compound (30 mmol) under inert atmosphere, was added the acyl chloride (1.0 mmol) or sulfonyl chloride (1.0 mmol). The reaction mixture was stirred at reflux temperature during 20 h. Upon completion, the reaction mixture was evaporated and purified by silica gel column chromatography with the appropriate mixture of *n*-hexane and ethyl acetate to afford the aromatic ketones or sulfones, which are all known compounds.