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Reactions on a Solid Surface. A Simple, Economical and Efficient Friedel−Crafts Acylation Reaction over Zinc Oxide (ZnO) as a New Catalyst

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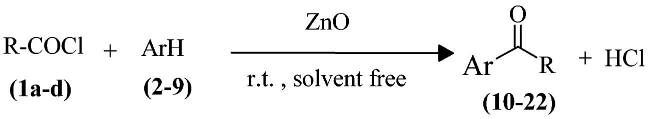
Abstract: Zinc oxide (ZnO) brings about a rapid Friedel−Crafts acylation of a range of activated and unactivated aromatic compounds such as anisole and chlorobenzene with acid chlorides in solvent-free conditions at room temperature. The ZnO powder can be reused up to three times after simple washing with dichloromethane.

Synthetic chemists continue to explore new methods to carry out chemical transformations. One of these new methods is to run reactions on the surface of solids. As the surfaces have properties that are not duplicated in the solution or gas phase, entirely new chemistry may occur. Even in the absence of new chemistry, a surface reaction may be more desirable than a solution counterpart, because the reaction is more convenient to run or a high yield of product is attained. For these reasons, surface synthetic organic chemistry is a rapidly growing field of study.

Experiments using these solid-phase catalysts generally have the following features: (i) it is often easy to isolate the products and to separate the catalyst; (ii) comparing the reaction conditions with those of related homogeneous reactions, they are so mild that a high yield of specific products and suppression of byproduct formation are expected; and (iii) selectivity and activity of the catalysts are often comparable to those of enzymes.[1] Several classes of solids have commonly been used for surface organic chemistry, including aluminas, silica gels, clays, etc.[2] Zinc oxide (ZnO), an inexpensive and commercially available inorganic solid, is certainly one of the most interesting of these solids. In this paper we described our work to reach a successful ZnO catalyst for Friedel−Crafts acylation reactions.

The Friedel−Crafts acylation of aromatic compounds is an important transformation in organic synthesis. In a typical Friedel−Crafts acylation reaction, an aromatic compound undergoes electrophilic substitution with an acylating agent in the presence of more than 1 equiv of acid catalyst (e.g., anhydrous $AlCl_3$) as a result of its complexation by the ketone product. The catalyst used cannot be easily recovered and recycled. Therefore, a large amount of toxic waste is generated. To solve this problem, some catalytic Freidel−Crafts acylations have recently been developed. $Ln(OTf)_3-LiCLO_4$,[3] $TiCl(OTf)_3-TfOH$,[4] $Re-Br(CO)_5$,[5] $LiClO_4$−acylhydride complex,[6] $FeCl_3$ over K10,[7] and clay catalysts[8] have been reported as catalysts for Friedel−Crafts acylation. In addition, the use of inorganic solid supported reagents[9] or solid acids[10] as catalysts, resulting in higher selectivity, easier work-up, and environmentally safe reactions, have been reported. For instance, HZSM-5 zeoilte has been reported to promote the liquid-phase acylation of anisole with carboxylic acids.[11] However, it presents limitations with regard to generality and efficiency. Recently, it was also shown that zinc powder promotes the acylation of activated and unactivated aromatics under microwave irradiation.[12]

SCHEME 1



Although numerous methods to achieve Friedel−Crafts acylation are known, newer methods continue to attract attention for their experimental simplicity and effectiveness. We have been interested in the development of methods for Friedel−Crafts acylation that (a) would avoid the use of added acids and bases, (b) would avoid aqueous workup and chromatographic purification, (c) are easy to perform, and (d) are economical for application to large-scale preparations. In this pursuit, we have recently reported on the use of ZnO for Beckmann rearrangement.[13] During the course of our studies aimed at developing solvent-free procedures,[13,14] we have now discovered that ZnO alone promotes a very efficient Friedel−Crafts acylation of activated and unactivated

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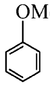
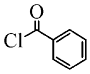
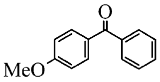
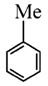
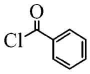
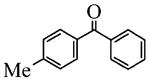
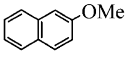
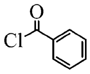
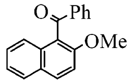
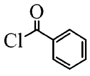
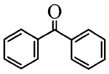
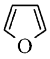
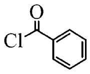
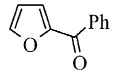
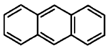
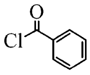
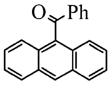
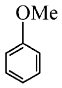
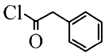
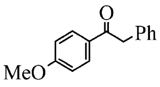
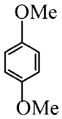
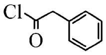
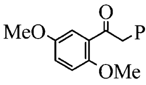
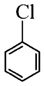
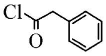
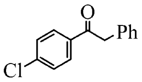
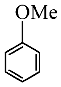
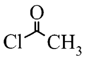
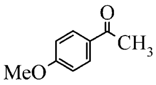
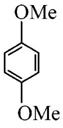
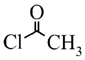
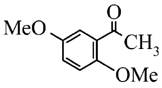
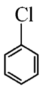
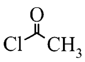
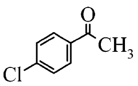
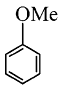
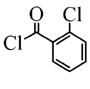
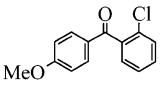
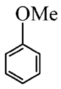
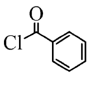
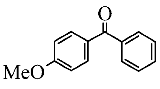
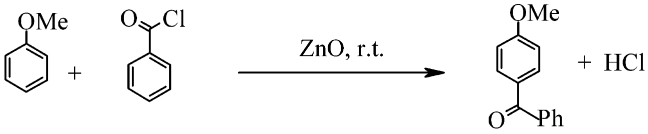
TABLE 1. Catalytic Friedel–Crafts Acylation

Entry	Substrate	Acid chloride	Product	Time(min.)	Yields[a] %
1	 **2**	 **1a**	 **10**	5	95
2	 **3**	 **1a**	 **11**	10	86
3	 **4**	 **1a**	 **12**	10	67[b]
4	 **5**	 **1a**	 **13**	120	50
5	 **6**	 **1a**	 **14**	10	94
6	 **7**	 **1a**	 **15**	120	50
7	 **2**	 **1b**	 **16**	5	98
8	 **8**	 **1b**	 **17**	5	92
9	 **9**	 **1b**	 **18**	5	85
10	 **2**	 **1c**	 **19**	5	97
11	 **8**	 **1c**	 **20**	10	90
12	 **9**	 **1c**	 **21**	10	87
13	 **2**	 **1d**	 **22**	10	95
14	 **2**	 **1a**	 **10**	5	94[c]

[a] Yields are the isolated compounds. [b] The reaction was carried out by grinding. [c] The reaction was carried out on a 100 mmol scale. **Caution**: the anisole (100 mmol) was added into a mixture of ZnO (4 gr, 50 mmol) and benzoyl chloride (100 mmol) in small portions.

TABLE 2. Reuse of ZnO



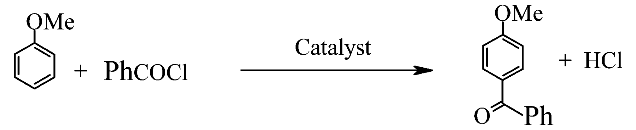
number of uses	yield (%)	recovery of ZnO
1	98	96
2	92	93
3	87	93

aromatic compounds with acyl chlorides in high yields at room temperature (Scheme 1). In a typical experiment, anisole **2** was added to a mixture of ZnO and phenylacetyl chloride **1b**. The mixture was kept at room temperature with occasional shaking for a certain period of time until the reaction was completed. The product was isolated by simple extraction of the solid mass by dichloromethane (CH_2Cl_2) followed by the usual workup.

The results of the Friedel–Crafts acylation of aromatic compounds are collected in Table 1. All of the aromatic compounds reacted very rapidly within 5–10 min. The reactions are remarkably clean, and no chromatographic separation is necessary to get the spectra-pure compounds except in a few cases (Table 1, entries 3 and 8) where some starting materials remained, the conversion being less than 100%. It was very exciting to find that unactivated benzenes such as chlorobenzene reacted smoothly in the presence of ZnO to afford the corresponding aromatic ketone in high yields (Table 1, entries 9 and 12). Acylation occurs exclusively at the position para to -OMe, -Me, and -Cl for all of the compounds studied in almost quantitative yields. However, in cases where the para positions are blocked (Table 1, entries 3, 8, and 11), the acyl group is introduced in the ortho position. This procedure is also good enough for the acylation of heterocyclic compounds such as furan (Table 1, entry 5), producing the corresponding 2-acylated product in excellent yield. The benzoylation of benzene and anthracene with benzoyl chloride themselves, volatile and less reactive, seemed more difficult to perform (Table 1, entries 4 and 6). Even after vigorous stirring for 120 min., the reaction was incomplete and only 50% yields of the corresponding acylated products were obtained. The Friedel–Crafts acylation of anisole with benzoyl chloride on a 100 mmol scale (Table 1, entry 14) proceeded just as well as the 1 mmol reaction. It is indeed gratifying to note that the reaction condition is mild enough not to induce any dealkylation of an ether residue ortho to the introduced acyl group (Table 1, entry 8) as observed in the acylation reaction with carboxylic acid catalyzed by BF_3.[16]

Furthermore, catalytic activity of the recovered catalyst (ZnO) was examined. As shown in Table 2, the yields of 4-methoxybenzophenone in second and third uses of the catalyst were almost same as that in the first use. In every case >90% of the ZnO was easily recovered from reaction mixture by simple washing with dichloromethane.

TABLE 3. Friedel–Crafts Acylation of Anisole with Benzoyl Chloride under Various Reaction Conditions



entry	catalyst	solvent	temp (°C)	time (min)	yield[b] (%)
1	$Sc(OTf)_3$–$LiClO_4$[3]	$MeNO_2$	50	60	90
2	graphite[17]	benzene	reflux	480	89
3	none	CH_2Cl_2	rt[a]	120	0
4	none	CH_2Cl_2	reflux	120	0
5	HgO	none	rt, 80 °C	120, 120	0, 0
6	Al_2O_3	none	rt, 80 °C	120, 120	0, 0
7	SiO_2	none	rt, 80 °C	120, 120	0, 0
8	Ag_2O	none	rt, 80 °C	120, 120	0, 24
9	Fe_2O_3	none	rt, 80 °C	120, 120	0, 32
10	ZnO	CH_3CN	rt	120	trace
11	ZnO	EtOAc	rt	120	trace
12	ZnO	THF	rt	120	trace
13	ZnO	$CHCl_3$	rt	120	41
14	ZnO	CH_2Cl_2	rt	120	45
15	ZnO	CH_2Cl_2	reflux	120	32
16	ZnO	none	rt	10	95

[a] Room Temperature. [b] Isolated yields.

No attempt has been made to probe the mechanism of the reaction. Mechanistically, it seems that $ZnCl_2$ could be the true catalyst generated in situ by the reaction of the ZnO with acid chloride and hydrogen chloride. In the absence of a chlorinating agent, for example, using an acid anhydride as the reagent and ZnO as the catalyst, acylation does not occur.

A comparison of the present protocol, using ZnO, with selected previously known protocols and other inorganic solids that were examined is collected in Table 3 to demonstrate that the present protocol is indeed superior to several of the other protocols. According to Table 3, Friedel–Crafts acylation of anisole is completed in less than 5 min at room temperature in 98% isolated yield using the present protocol. Most of the other protocols listed either take a longer time for completion, require prior preparation of the catalyst support, or use toxic solvents with generally reduced isolated yields (entries 1 and 2). We also surveyed a variety of inorganic solids as catalyst and examined the effect of the temperature and solvents on the yield of the corresponding acylated product (entries 3–9). For comparison, when HgO, Al_2O_3, SiO_2, Ag_2O, or Fe_2O_3 was used in place of ZnO in the reaction of anisole with benzoyl chloride at room temperature, reactions were ineffective. In fact, only 24% and 32% progress were observed when Ag_2O and Fe_2O_3 were used at 80 °C, respectively. We also examined the effects of solvents in this reaction. Although the reaction proceeded smoothly in chloroform or dichloromethane, only 41% and 54% yields of the product were detected (entries 10–15). Thus, ZnO was found to be the better choice for this reaction.

In conclusion, we have described a novel and highly efficient solvent-free protocol for Friedel–Crafts acylation of aromatic compounds using nontoxic and inexpensive ZnO powder. The advantages of this environmentally benign and safe protocol include a simple reaction setup not requiring specialized equipment, very mild reaction

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conditions, high product yields, very short reaction times, and the elimination of solvents.

Experimental Section

General Procedure. An aromatic compound (1 mmol) was added to a mixture of ZnO (powder, 0.04 g, 0.5 mmol) and acid chloride (1 mmol) at room temperature and stirred with a magnetic stirrer. Color (usually pink, but in few cases green or blue) developed immediately and darkened with progress of the reaction. The reaction mixture was kept at room temperature with occasional stirring for a certain period of time (Table 2) as required to complete the reaction (monitored by TLC). The solid mass was then eluted with dichloromethane (CH_2Cl_2) (20 mL), and the dichloromethane extract was then washed with an aqueous solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of solvent furnished practically pure the corresponding product. The identity of these compounds was easily established by comparison of their ^1H NMR spectra with those of authentic sample.

All of the acylated products are known compounds and characterized easily by comparison with authentic samples (IR, ^1H NMR, mp, bp).[12,15]

1-(2,5-Dimethoxy)-2-phenyl-1-ethanone (17). ^1H NMR ($CDCl_3$): δ 3.80 (s,6H), 4.35 (s,2H), 6.88−7.60 (8H,Ar−H). IR (neat): 1697 (C═O) cm^{-1}.

2-Chlorophenyl (4-Methoxy phenyl) Methanone: ^1H NMR ($CDCl_3$): δ 3.82 (s,3H), 6.94 (d,2H, Ar−H), 7.27−7.45 (4H,Ar−H), 7.80 (d, 2H, Ar−H). IR (KBr): 1688 (C═O) cm^{-1}.

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Supporting Information Available: Complete experimental procedures and relevant spectra (^1H NMR spectra) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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