Friedel–Crafts Acetylation, Propionylation, and Butyrylation of Toluene Catalyzed by Solid Superacids

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The liquid–solid phase acetylation of toluene with acetic anhydride was carried out over solid superacids of sulfated metal oxides (SO_4/MeO_x) and supported metal oxides (Me^1O_x/Me^2O_y) selected from the results in the benzoylation of toluene with benzoic anhydride [K. Arata, H. Nakamura, and M. Shouji, *Appl. Catal. A: General*, **197**, 213 (2000)]. The reaction was conducted by adding dropwise a mixture of 2 mmol of acetic anhydride and 2 mL of toluene onto 0.5 g of catalyst suspended in 13 mL of toluene with stirring at 110 °C in the first period of 30 min, followed by stirring the mixture for 2 h. The yields of 2′-, 3′-, and 4′-methylacetophenones in the distribution of 9–10% 2′-, 1–2% 3′- and 89–90% 4′-isomers were 24 and 13% for the sulfated metal oxides of SO_4/ZrO_2 and SO_4/SnO_2, those by Pt and Ru promoted sulfated zirconias (Pt-, Ru-SO_4/ZrO_2) being 21 and 28%, respectively. The supported metal oxides of Fe_2O_3/ZrO_2 and WO_3/ZrO_2 gave yields of 18 and 15%, respectively. The propionylation and butyrylation of toluene with propionic and butyric anhydrides were performed over SO_4/ZrO_2, SO_4/SnO_2, Pt-SO_4/ZrO_2, and Ru-SO_4/ZrO_2; the yields of 7–9% *o*- and 91–93% *p*-isomers were 31, 26, 32, and 44% for propionylation and 46, 29, 44, and 55% for butyrylation, respectively. The SO_4/ZrO_2 catalyst gave a 100% yield of 4′-methoxyacetophenone for the acetylation of anisole with acetic anhydride.

The catalytic acylation of aromatics via the Friedel–Crafts reaction remains a prerequisite challenge to green technology. Traditional methods depend on the use of at least stoichiometric quantities of Lewis acids, such as aluminium trichloride and boron trifluoride, because the Lewis catalysts are consumed by coordination with the formed aromatic ketones.[1,2] A large amount of the acids and their waste matter after work-up procedures cause serious environmental problems; the use of toxic Friedel–Crafts catalysts involves many problems to be solved. As a goal, there have been several efforts to conduct the reaction using catalytic amounts of acidic promoters.[3–8] Recently, Kobayashi and co-workers found rare earth metal trifluoromethanesulfonates, $RE(OTf)_3$, to be efficient catalysts for acylation;[9] a catalytic amount of the materials was easily recovered and reused. Yadav and Pujari synthesized 4′-chlorobenzophenone, a pharmaceutical intermediate, via the acylation of benzene with 4-chlorobenzoyl chloride over sulfated zirconia (SO_4/ZrO_2) as a catalyst,[10] though the acid in place of the acid chloride as the acylating agent was better for a genuinely environmental trend.

Solid superacids of sulfated metal oxides (SO_4/MeO_x) and supported metal oxides (Me^1O_x/Me^2O_y) were synthesized by the addition of sulfate species to oxide surfaces of Fe, Ti, Zr, Hf, Sn, Al, and Si, or by supporting SnO_2, TiO_2, Fe_2O_3, and ZrO_2 with WO_3 and ZrO_2 with MoO_3 and B_2O_3,[11,12] metal-promoted superacids, which are also being prepared.[13–15] A previous paper reported on a comparative study of those superacids for the benzoylation of toluene with benzoic anhydride and benzoyl chloride in the liquid–solid phase.[16] A relationship was obtained between the highest acid strength of the catalysts and the acylated yields. Most of the superacids gave satisfactory yields of 2′-, 3′-, and 4′-methylbenzophenones with the acid anhydride as the acylating agent. In consideration of the results, several catalysts were also examined in a less reactive acylation: the acetylation of toluene with acetic anhydride or acetyl chloride. However, satisfactory results were not obtained.

Chiche and others reported on the acylation of toluene and *p*-xylene by various carboxylic acids catalyzed by a Y-faujasite-type zeolite exchanged with the Ce^{3+} cation.[17] In a plot of the yield as a function of the number of carbon atoms of carboxylic acids, the yield increased linearly as the hydrocarbon chain was lengthened. This phenomenon is not encountered in classical Friedel–Crafts reactions, and shows acetylation to be the most difficult acylation, because of a difficulty in the formation of an intermediate acetyl cation ($MeCO^+$) from alkyl chain acid anhydrides and halides. Thus, liquid–solid acetylation is an attractive challenge for clean technology as well as for organic synthesis; the present paper is concerned with a systematic study of several superacids for the acetylation of toluene with acetic anhydride, together with acylations with longer hydrocarbon chains, propionylation and butyrylation at mild temperatures below reflux operating in a batch mode. To the best of our knowledge, the heterogeneous acetylation of toluene using solid acidic promoters has not been reported in detail.

Experimental

Catalysts. Preparation of Zirconium(Ⅳ) and Tin(Ⅳ) Hydroxides: 1. $Zr(OH)_4$. The hydroxide was obtained by hydrolyzing $ZrOCl_2$ with aqueous ammonia to pH 8 at a temperature of 60–70 °C; the precipitates were washed several times with hot water, and finally dried.

2. $Sn(OH)_4$. Aqueous ammonia was added into a solution of

$SnCl_4$ in water with stirring at 60 °C, the final pH of the solution being 8. The precipitates were washed by decantation five times using hot water, and dried.

The precipitated hydrogels were dried at 100 °C for 24 h and powdered to below 100 mesh.

Sulfate Treatment of Metal Hydroxides: Materials prepared as described above were treated with sulfate ions by exposing 2 g of the hydroxide in 30 mL of aqueous sulfuric acid on a glass filter for 1 h, followed by filtering, drying them at room temperature, and finally calcining. The concentration of H_2SO_4 was 0.5 and 3 M ($1\ M = 1\ mol\,dm^{-3}$) for the hydroxides of Zr and Sn, respectively; the calcination temperature was 550 °C for Sn and 600 °C for Zr. The prepared catalysts are indicated as SO_4/ZrO_2 and SO_4/SnO_2.

Two more SO_4/ZrO_2 catalysts were prepared. One was prepared by calcining sulfated zirconia of Wako Pure Chemical Industries, Ltd., at 550 °C. The other was prepared by powdering zirconium hydroxide, XZO 632/03, of MEL Chemicals (dried at 100 °C for 24 h), followed by treating with 0.5 M H_2SO_4 and calcining at 600 °C. The former catalyst was denoted as SO_4/ZrO_2-1 and the latter as SO_4/ZrO_2-2; thus, the sulfated zirconia prepared from $ZrOCl_2$ was denoted as SO_4/ZrO_2-3.

Preparations of Pt- and Ru-Added Sulfated Zirconias: Pt-SO_4/ZrO_2-1, -2, and -3 were obtained by treating the corresponding zirconium hydroxides with 0.5 M H_2SO_4, followed by drying, impregnating with aqueous $H_2PtCl_6 \cdot 6H_2O$ (to obtain 3 wt% Pt in the final catalyst after calcination), evaporating residual water, drying, and calcining in air at 600 °C.

Ru-SO_4/ZrO_2-2 was obtained by impregnating $Zr(OH)_4$ (XZO 632/03) with an aqueous solution of $RuCl_3 \cdot nH_2O$, followed by evaporating residual water, drying at 300 °C for 3 h, treating with 0.5 M H_2SO_4, drying, and finally calcining at 550 °C, the concentration being 3 wt% Ru, based on the hydroxide.

All of the catalysts were calcined in Pyrex glass tubes in air for 3 h and sealed in ampoules while hot to avoid humidity until use.

Preparation of Superacids by Metal Oxides: WO_3/ZrO_2-2 was obtained by impregnating $Zr(OH)_4$ (XZO 632/03) with aqueous ammonium metatungstate $[(NH_4)_6(H_2W_{12}O_{40})]$, followed by evaporating water at room temperature, drying, and calcining at 800 °C for 3 h. The concentration was 15 wt% W metal based on the hydroxides. Fe_2O_3/ZrO_2-2 was obtained by impregnating $Zr(OH)_4$ (XZO 632/03) with an aqueous solution of $Fe(NO_3)_3$, followed by evaporating residual water, drying at 300 °C for 3 h, treating with 0.5 M H_2SO_4, drying, and calcining at 700 °C for 26 h (2 wt% Fe).

The calcination at temperatures above 700 °C was performed in a ceramic crucible, followed by calcining in Pyrex glass tubes at 500 °C for 1 h and sealing in ampoules until use.

Reaction Procedure. The acetylation was carried out with a mixture of 15 mL (141 mmol) of toluene (purified by distillation before use), 2 mmol of acetic anhydride (0.204 g), 0.5 g of catalyst, and 0.185 g (1 mmol) of tridecane as an internal standard with stirring at 110 °C under an argon atmosphere; a mixture of 0.204 g of the acid and 2 mL of toluene was added dropwise with stirring onto catalyst suspended in 13 mL of toluene in the first period of 30 min, followed by stirring the mixture for 2–3 h. A small amount of the sample was withdrawn periodically with a 1 mL syringe, diluted with ethyl acetate, separated from the catalyst by filtration, and analyzed by gas–liquid chromatography with a FID detector using a 25 m column of OV-1701 BONDED in the temperature range from 80 to 220 °C at the programmed rate of 5 °C/min. The product isomers were identified by a comparison of their spectral data and retention times in GLC with those of authentic samples. Since toluene was in excess, the yields were based on the acylating reagents.

Identification and Isolation of the Product. ^{1}H NMR spectra were recorded on a JEOL JNM-EX270 spectrometer. Silica-gel column chromatography was performed using Merck Kiesel 60 (70–230 mesh).

2′-Methylpropiophenone. ^{1}H NMR ($CDCl_3$) δ 7.63–7.64 (m, 1H), 7.31–7.36 (m, 1H), 7.16–7.27 (m, 2H), 2.92 (q, $J = 7.3$ Hz, 2H), 2.49 (s, 3H), 1.19 (t, $J = 7.3$ Hz, 3H).

4′-Methylpropiophenone. ^{1}H NMR ($CDCl_3$) δ 7.85 (d, $J = 8.25$ Hz, 2H), 7.24 (d, $J = 8.25$ Hz, 2H), 2.88 (q, $J = 7.3$ Hz, 2H), 2.31 (s, 3H), 1.13 (t, $J = 7.3$ Hz, 3H).

2′-Methylbutyrophenone. ^{1}H NMR ($CDCl_3$) δ 7.60 (d, $J = 7.26$ Hz, 1H), 7.16–7.39 (m,3H), 2.87 (t, $J = 7.26$ Hz, 2H), 2.48 (s, 3H), 1.74 (hex, $J = 7.26$ Hz, 2H), 0.99 (t, $J = 7.26$ Hz, 3H).

4′-Methylbutyrophenone. ^{1}H NMR ($CDCl_3$) δ 7.86 (d, $J = 8.25$ Hz, 2H), 7.25 (d, $J = 8.25$ Hz, 2H), 2.92 (t, $J = 7.26$ Hz, 2H), 2.41 (s, 3H), 1.76 (hex, $J = 7.26$ Hz, 2H), 1.00 (t, $J = 7.26$ Hz, 3H).

4′-Methoxyacetophenone. ^{1}H NMR ($CDCl_3$) δ 7.93 (d, $J = 8.9$ Hz, 2H), 6.92 (d, $J = 8.9$ Hz, 2H), 3.86 (s, 3H), 2.55 (s, 3H).

Results and Discussion

Among solid superacids of sulfated and supported metal oxides, SO_4/ZrO_2-1 showed the highest activity for the benzoylation of toluene with benzoic anhydride,[16] and thus acetylation was carried out under common solid–liquid conditions with a mixture of 15 mL of toluene, 2 mmol of acetic anhydride, and 0.5 g of the catalyst with stirring at 110 °C for 4 h, though the yield was quite low, 8% (Entry 1 in Table 1). Supplementary examinations were tried several times, but the results were identical with the above. Most of the reactions did not show a continual increase of yield with time, and the catalyst failed to react further after 30–60 min. A question arises concerning the deactivation of the catalyst, or the decomposition of the anhydride, during the early stage of the reaction. Thus, the reaction conditions were changed; the results are summarized in Table 1.

A catalyst suspended in 10 mL of toluene was added dropwise with stirring into a mixture of 5 mL of toluene and the anhydride (2 mmol) in the first period of 5 or 20 min, followed by continual stirring; even if the period was extended, the yields hardly increased (Entry 2, 3). The anhydride mixed with 2 mL of toluene was added dropwise into a mixture of toluene (13 mL) and the catalyst for periods of 12 and 30 min, and the yields were also promoted (Entry 4, 5); in particular, the enhancement by a longer period of 30 min was three times, 24%. A long time of the dropping was tried; that is, a mixture of 10 mL of toluene and the anhydride was added into the remaining toluene (5 mL)–catalyst solution during a period of 60 min, though the result was not the expected observation (Entry 6).

In consideration of the above results, it is proposed that CH_3COOH derived from acetylation has an effect on the subsequent reaction. Following the procedure of Entry 5, the reaction was performed with the anhydride (2 mmol) mixed with acetic acid (1.7 mmol) or with CH_3COOH (2 mmol), without

Table 1. Acetylation of Toluene with Acetic Anhydride Catalyzed by SO_4/ZrO_2-1 at 110 °C under Various Conditions

Entry	Time/h	Yield/%	Condition
1	4	8	Stirring of toluene–Ac_2O–catalyst
2	3	16	Dropping of catalyst–toluene into toluene–Ac_2O for 5 min
3	3	10	Dropping of catalyst–toluene into toluene–Ac_2O for 20 min
4	3	14	Addition of Ac_2O–toluene into toluene–catalyst for 12 min
5	3	24	Addition of Ac_2O–toluene into toluene–catalyst for 30 min
6	3	9	Addition of Ac_2O–toluene into toluene–catalyst for 60 min
7	2	1	Addition of Ac_2O–AcOH–toluene following Entry 5
8	2	Trace	Addition of AcOH–toluene following Entry 5
9	3	0.3	Stirring of toluene–Ac_2O–catalyst–molecular sieves
10	3	0.4	Stirring of toluene–Ac_2O–catalyst–silica gel
11	4	1	Addition of Ac_2O–toluene into nitrobenzene–catalyst
12	4	2	Addition of Ac_2O–toluene into chlorobenzene–catalyst
13	4	0	Addition of AcOEt–toluene following Entry 5

Table 2. Acetylation of Toluene with Acetic Anhydride over Various Solid Catalysts at 110 °C for 2 h

Catalyst	Yield/%	Isomers/%		
		o-	*m*-	*p*-
SO_4/ZrO_2-1	24	11	1	88
SO_4/ZrO_2-2	22	9	1	90
SO_4/ZrO_2-3	22	9	1	90
SO_4/SnO_2	13	9	2	89
Pt-SO_4/ZrO_2-1	14	9	2	89
Pt-SO_4/ZrO_2-2	19	9	1	90
Pt-SO_4/ZrO_2-3	21	9	2	89
Ru-SO_4/ZrO_2-2	28	9	2	89
Fe_2O_3/ZrO_2-2	18	10	1	89
WO_3/ZrO_2-2	15	8	1	91

Table 3. Acylation of Toluene with Propionic and Butyric Anhydrides at 110 °C for 2 h

Catalyst	Propionylation			Butyrylation		
	Yield/%	Isomers/%		Yield/%	Isomers/%	
		o-	*p*-		*o*-	*p*-
SO_4/ZrO_2-1	31	8	92	46	9	91
SO_4/SnO_2	26	7	93	29	7	93
Pt-SO_4/ZrO_2-2	32	7	93	44	8	92
Ru-SO_4/ZrO_2-2	44	7	93	55	8	92

the anhydride, as the acylating agent; the expected results were observed (Entry 7, 8). The inactivity with the acid is based on its coordination with an acid site on the catalyst surface as a result of lowering the acidity for acetylation. Thus, the effect of the adsorbent for produced CH_3COOH was examined; acetylation was carried out with stirring the mixture along with 2 g of dried molecular sieve 4A or silica gel, but no reaction progressed (Entry 9, 10). The anhydride was probably adsorbed on the adsorbents.

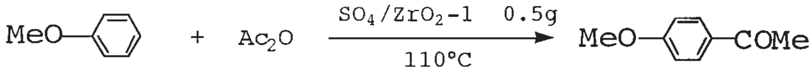
In the homogeneous Friedel-Crafts reaction, the reaction is frequently performed using solvents, such as nitromethane and acetonitrile.[1,2] In order to raise the yield, acetylation was tried in nitrobenzene or chlorobenzene as a solvent following the procedure of Entry 5: the addition of Ac_2O (2 mmol)–toluene (2 mL) into a mixture of solvent (13 mL) and catalyst, though the results were not satisfactory (Entry 11, 12) because of a probable coordination of unpaired electrons of nitrobenzene or chlorobenzene with the catalyst surface for lowering the acidity. Finally, the acetylation with ethyl acetate as the acylating reagent, without producing CH_3COOH during the reaction, was examined as a result of the ineffectiveness (Entry 13) of acylations using esters as the acylating agent, usually being difficult.[18]

Since the procedure of Entry 5 gave the highest yield, the acetylation following the method was performed over other sulfated zirconias, and their Pt or Ru promoted materials along with SO_4/SnO_2, Fe_2O_3/ZrO_2, and WO_3/ZrO_2, whose catalysts were highly effective for the benzoylation of toluene with benzoic anhydride; the results are given in Table 2. Although yields higher than 24%, obtained by SO_4/ZrO_2-1, were expected, only Ru-SO_4/ZrO_2-2 showed a expected value of 28%. In benzoylation, the preparation method of the catalyst largely controlled the catalytic activity, particularly for the SO_4/ZrO_2 matter, though the present acylation did not show any difference in the yields. Although a modification of SO_4/ZrO_2 by the addition of Pt and Ru also led to a large promotion of activity for benzoylation, the present results were not better than expected.

The products were 2′-, 3′-, and 4′-methylacetophenones, and the distribution was not much varied: 9–10% 2′-, 1–2% 3′-, and 89–90% 4′-isomers. The predominant para-substitution is similar to that by the usual homogeneous reaction.

As described in the introduction, acetylation is the most difficult acylation because of the formation of its intermediate ($MeCO^+$). Therefore, more reactive acylations by acylating reagents with longer hydrocarbon chains, propionylation and butyrylation, were performed with several catalysts (Table 2); SO_4/ZrO_2-1, SO_4/SnO_2, Pt-SO_4/ZrO_2-2, and Ru-SO_4/ZrO_2-2 were examined in reactions of toluene with propionic and butyric anhydrides under the same conditons as the acetylation of Entry 5 in Table 1 (the results in Table 3). All of the catalysts gave yields higher than those of acetylation for pro-

Table 4. Acetylation of Anisole



Entry	Time/h	Yield/%	Condition
1	1	78	Entry 5 in Table 1
	2	90	
2	1	100	Entry 1 in Table 1

pionylation as well as butyrylation; the latter was higher than the former in each case. The Ru-SO_4/ZrO_2-2 catalyst again showed the highest yields in both acylations, as was observed with acetylation. The reactivity with acylating reagents is $(PrCO)_2O > (EtCO)_2O > (MeCO)_2O$, which agrees with their intermediate stability of $PrCO^+ > EtCO^+ > MeCO^+$.

The product distribution was not varied, 7–9% *o*- and 91–93% *p*-isomers for the both reactions, 4′-methylpropiophenone and 4′-methylbutyrophenone, and their meta-isomers were not analyzed because of minor yields.

The present catalyst was examined in a more reactive acetylation, the acetylation of anisole with acetic anhydride; Table 4 gives the results for catalysis by SO_4/ZrO_2-1. It can be seen how effective the present catalyst is for anisole, in comparison with toluene. In this case, a quantitative yield of methoxyacetophenone was obtained by the usual, most simple, procedure of liquid–solid phase reactions, the stirring of a suspended mixture. The product was 4′-methoxyacetophenone, and other isomers were not detected, as shown in the literature.[9]

In conclusion, this work has addressed a green chemistry toward environmentally benign processes, where solid superacids lead to catalysts for a new liquid–solid acetylation of toluene with acetic anhydride, one of the most difficult Friedel–Crafts acylations. The process was effective in the propionylation and butyrylation of toluene with propionic and butyric anhydrides, giving yields higher than those of acetylation, the latter being higher than the former in yield. The acetylation of anisole with acetic anhydride over sulfated zirconia was 100% active in yield and selective towards *p*-methoxyacetophenone.

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