

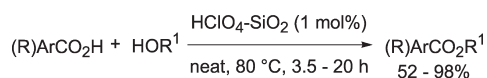
Protic Acid Immobilized on Solid Support as an Extremely Efficient Recyclable Catalyst System for a Direct and Atom Economical Esterification of Carboxylic Acids with Alcohols

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<p>Ar = Aromatic/Heteroaromatic; R = Alkyl/Arylalkyl/Cycloalkyl; R¹ = Alkyl/Alkenyl/Alkynyl/Arylalkyl/Cycloalkyl</p>

A convenient and clean procedure of esterification is reported by direct condensation of equimolar amounts of carboxylic acids with alcohols catalyzed by an easy to prepare catalyst system of perchloric acid immobilized on silica gel (HClO₄-SiO₂). The direct condensation of aryl, heteroaryl, styryl, aryl alkyl, alkyl, cycloalkyl, and long-chain aliphatic carboxylic acids with primary/secondary alkyl/cycloalkyl, allyl, propargyl, and long-chain aliphatic alcohols has been achieved to afford the corresponding esters in excellent yields. Chiral alcohol and *N*-*t*-Boc protected chiral amino acid also resulted in ester formation with the representative carboxylic acid or alcohol without competitive *N*-*t*-Boc deprotection and detrimental effect on the optical purity of the product demonstrating the mildness and chemoselectivity of the procedure. The esters of long-chain (> C₁₀) acids and alcohols are obtained in high yields. The catalyst is recovered and recycled without significant loss of activity. The industrial application of the esterification process is demonstrated by the synthesis of prodrugs of ibuprofen and a few commercial flavoring agents. Other protic acids such as H₂SO₄, HBr, TfOH, HBF₄, and TFA that were adsorbed on silica gel were less effective compared to HClO₄-SiO₂ following the order HClO₄-SiO₂ ≫ H₂SO₄-SiO₂ > HBr-SiO₂ > TfOH-SiO₂ ≫ HBF₄-SiO₂ ≈ TFA-SiO₂. When HClO₄ was immobilized on other solid supports the catalytic efficiency followed the order HClO₄-SiO₂ > HClO₄-K10 > HClO₄-Al₂O₃ (neutral) > HClO₄-Al₂O₃ (acidic) > HClO₄-Al₂O₃ (basic).

Introduction

Organic esters are important products/intermediates in the chemical and pharmaceutical industries where they are extensively used for the production of fragrances, polymers, polyesters, plasticizers, fatty acids, and paints which are considered as high production-volume (HPV) chemicals.¹ Esterification provides a means of masking carboxylic acid

group,² constitutes 28% of all the transformations involved in drug synthesis,³ and amounts to one-fourth of the bulk reactions in the manufacturing of drugs and pharmaceuticals.⁴ These advantages make esterification one of the most important organic reactions to occupy a prominent place in the desire to develop benign and sustainable methodologies⁵ for industrial applications.

Dialkyl sulfates are popular as *O*-alkylation agents⁶ and chemoselective carboxyl *O*-alkylation with dialkyl sulfates is

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an alternative to the diazoalkane protocol.⁷ However, the lack of commercial availability of different dialkyl sulfates limits their application to methyl/ethyl esters and indicates the necessity for better and general alkylating agents.

Dimethyl carbonate (DMC) is considered a safer methylating reagent⁸ and has been used for reaction with nucleophiles such as phenols, primary amines, sulfones, thiols, and active methylene derivatives.⁹ But the lack of commercial availability of a variety of dialkyl carbonates is a disadvantage for their general use. Although DMC can be considered an environmentally benign compound, the reported reaction conditions for methylation with DMC are not apparently green as these require high temperature (> 160 °C) that implies an autogenic pressure (> 3 bar). The reactions are carried out either under continuous flow or batch reactors in the presence of base catalysts. The limited reports on carboxyl-*O*-methylation with DMC involve the treatment in the presence of NaY faujasite at 165 °C in a stainless-steel autoclave for 13–20 h,¹⁰ heating in the presence of stoichiometric amounts of DBU under reflux,¹¹ or circulating the reaction mixture in a microwave reactor preheated to 160 °C at 20 bar under microwave irradiation.¹²

The condensation of a carboxylic acid with alcohol appears to be the most straightforward and general route for the synthesis of esters. However, the difficulty arises due to the reversibility of the reaction. Therefore, it necessitates the need to use excess amounts of one of the reactants over the other or the continuous removal of the water formed to drive the reaction equilibrium toward the product (ester). The former process is not preferred on the grounds of “atom economy”.¹³ Water removal by azeotropic distillation or by the use of dehydrating agents does not make the desired conversion/yield easy to achieve. An ideal esterification process should be the one that offers quantitative conversion/yield from molar equivalents (1:1 ratio) of the carboxylic acid and the alcohol and avoids the necessity of a dehydration process. Thus, efforts have been directed toward esterification with 1:1 ratio of carboxylic acid and the alcohol.¹⁴ However, some of these methodologies still require heating (azeotropic water removal) in solvents such as *o*-xylene, 1,3,5-mesitylene, or toluene^{14a–c} and dehydrating agents.^{14a,d} The other esterification procedure involving heating in Brønsted acidic ionic liquids as solvent^{14e,f} or using surfactant-combined^{14g}/Brønsted acidic ionic liquid^{14h} catalysts is limited to a few simple carboxylic acids

and primary alcohols as substrates. The carboxylic acid activation strategies¹⁵ require stoichiometric amounts of additional reagent such as tetramethylfluoroformamidinium hexafluorophosphate (TFFH) (not available commercially and requires special efforts for preparation) or di-*tert*-butyl dicarbonate and toxic 4-dimethylaminopyridine (DMAP)¹⁶ as the catalyst. The Lewis acid catalyzed decarboxylative esterification of carboxylic acids with dialkyl dicarbonates¹⁷ is not atom economical and requires costly reagents. Therefore, the search remains for a general and practical esterification procedure.¹⁸

We were influenced by the awareness of the use of solid acids¹⁹ and chemical processes on solid surfaces²⁰ as environmentally friendly approaches in organic synthesis. In pursuit of designing/choosing a suitable catalyst system, we realized that the usual homogeneous catalysts are often destroyed during product isolation and this “once through” utilization of the catalyst can result in unacceptably high manufacturing costs. A heterogeneous catalyst system, on the other hand, may be easily recovered by filtration and recycled. This has advantages in that the extra processing steps are eliminated and spent catalyst disposal is minimized.

To this endeavor we discovered two novel catalyst systems, e.g., perchloric acid immobilized on silica gel (HClO₄–SiO₂) and fluoroboric acid immobilized on silica gel (HBF₄–SiO₂),²¹ that were found to be highly effective for various organic transformations.^{21,22} These catalyst systems (HClO₄–SiO₂ and HBF₄–SiO₂) are/were not commercially available and were invented by Chakraborti and Gulhane and used for the first time for organic synthesis.²¹ We were delighted to observe that soon after the original work on its invention Chakraborti’s novel catalyst system HClO₄–SiO₂^{21a,c} caught the attention of other researchers globally who started applying HClO₄–SiO₂ as catalyst for a large variety of organic reactions/syntheses (e.g., amidoalkylation of naphthols, construction of heterocyclic scaffolds, homoallyl amines, α -bromo and β -amino/sulfido carbonyl compounds, trisubstituted alkenes, acylals, carbohydrates, etc.).²³ We now report HClO₄–SiO₂ as an extremely efficient and reusable catalyst system for a general and practical esterification process by direct condensation of carboxylic acids with alcohols in atom economical fashion.²⁴

Results and Discussion

Various protic acids adsorbed on solid supports were studied for their efficiency toward the esterification of

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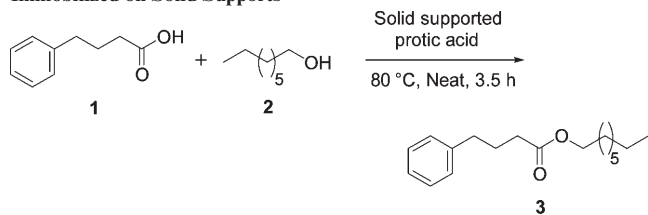
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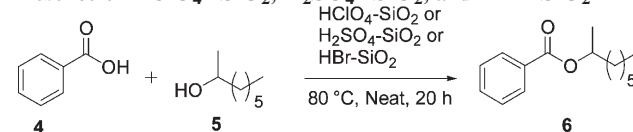
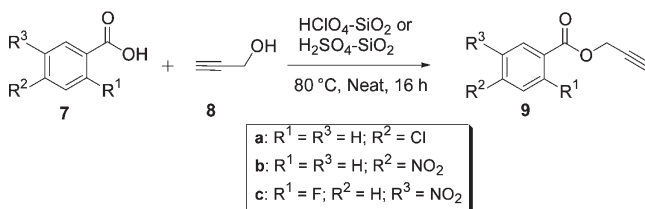
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TABLE 1. Direct Esterification of **1** with **2** Catalyzed by Protic Acids Immobilized on Solid Supports^a

entry	catalyst	yield (%) ^b
1	SiO ₂	nil ^c
2	Montmorillonite K10	15 ^c
3	Montmorillonite KSF	30 ^c
4	Al ₂ O ₃ (neutral)	nil ^c
5	Al ₂ O ₃ (acidic)	nil ^c
6	Al ₂ O ₃ (basic)	nil ^c
7	HClO ₄ -SiO ₂	98
8	HClO ₄ -K10	90
9	HClO ₄ -Al ₂ O ₃ (neutral)	85
10	HClO ₄ -Al ₂ O ₃ (acidic)	65 ^c
11	HClO ₄ -Al ₂ O ₃ (basic)	60 ^c
12	H ₂ SO ₄ -SiO ₂	95
13	HBr-SiO ₂	95
14	HF-SiO ₂	15 ^c
15	TFA-SiO ₂	10 ^c
16	TfOH-SiO ₂	85

^aThe mixture of **1** (2.5 mmol) and **2** (2.5 mmol) in the presence of the catalyst (1 mol %) was heated for 3.5 h at 80 °C under solvent-free conditions. ^bIsolated yield of purified **3**. ^cThe unreacted starting materials remained unchanged.

4-phenylbutyric acid (**1**) with equimolar amounts of *n*-octanol (**2**) in the absence of any solvent at 80 °C (Table 1). The desired ester *n*-octyl 4-phenylbutyrate (**3**) was obtained 98%, 95%, and 95% yields in the presence of HClO₄-SiO₂, H₂SO₄-SiO₂,^{24,25a,b} and HBr-SiO₂ (entries 7, 12, and 13, Table 1), respectively. The use of Montmorillonite K10/KSF provided lesser yield (90%) but the use of other solid supports such as alumina^{24,25a,c} (neutral/basic/acidic) in place of silica gel was found to be far less effective. The solid supports alone did not exhibit any significant catalytic

SCHEME 1. Direct Condensation of **4** and **5** To Form **6** in the Presence of HClO₄-SiO₂, H₂SO₄-SiO₂, and HBr-SiO₂**SCHEME 2.** Direct Condensation of **7a-c** and **8** Catalyzed by HClO₄-SiO₂ and H₂SO₄-SiO₂ To Form **9a-c**

effect (entries 1–6). It is likely that the role of silica gel may not merely be to provide the surface area. The significantly superior catalytic activity of the perchloric acid adsorbed on silica gel than on other solid supports such as alumina (acidic/basic) indicates that silica gel enhances the Bronsted acidic property. However, the simple role of silica as a water sequestering agent may be ruled out since perchloric acid adsorbed on other solid supports exhibits inferior catalytic properties. Thus, while alumina is known for its dehydrating property, the inferior catalytic activity of perchloric acid adsorbed on alumina (acidic/basic) compared to that of HClO₄-SiO₂ does not substantiate that silica gel in HClO₄-SiO₂ serves only to sequester the water.

As comparable results were obtained in using HClO₄-SiO₂, H₂SO₄-SiO₂, and HBr-SiO₂, we decided to judge the most effective catalyst system. For this, the Fischer condensation of benzoic acid (**4**) (2.5 mmol) (as the carbonyl carbon of aromatic carboxylic acid is less electrophilic compared to that in **1**) with 2-octanol (**5**) (2.5 mmol) (a representative sterically hindered alcohol compared to **2**) was considered as the model (Scheme 1). The desired product octan-2-yl benzoate (**6**) was obtained in 95%, 90%, and 40% yields, respectively, at 80 °C after 20 h.

Further efforts were made for the evaluation of mildness and efficiency of the HClO₄-SiO₂ and H₂SO₄-SiO₂ for the esterification of 4-chlorobenzoic acid (**7a**), 4-nitrobenzoic acid (**7b**), and 2-fluoro-5-nitrobenzoic acid (**7c**) [representatives of moderately and strongly deactivated aromatic carboxylic acids compared to **4**] with an acid sensitive alcohol propargyl alcohol (**8**) under identical reaction conditions (Scheme 2). The desired esters prop-2-ynyl 4-chlorobenzoate (**9a**), prop-2-ynyl 4-nitrobenzoate (**9b**), and prop-2-ynyl 2-fluoro-5-nitrobenzoate (**9c**) were obtained in 80%, 79%, and 78% yields, respectively, in using HClO₄-SiO₂ compared to 20%, 46%, and 38% yields of the corresponding products for the H₂SO₄-SiO₂ catalyzed reactions and established that HClO₄-SiO₂ is the most effective catalyst system.

Having on hand HClO₄-SiO₂ as an efficient catalyst for direct esterification, efforts were made to optimize the reaction conditions by varying the various reaction parameters such as catalyst loading and reaction conditions (e.g., reaction temperature and solvent). For the determination of the effective amount of HClO₄-SiO₂, the reaction of

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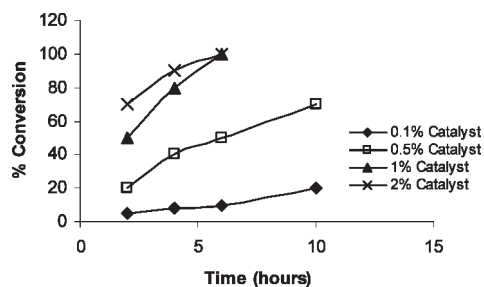


FIGURE 1. Graphical representation of the time required for direct condensation of **10** (2.5 mmol) with **11** (2.5 mmol) in the presence of various amounts of $\text{HClO}_4\text{-SiO}_2$ to form **12**.

dihydrocinnamic acid (**10**) with allyl alcohol (**11**) was considered as the model. When the reactions were carried out with lower amounts of the catalyst (0.1 and 0.5 mol %) either trace amounts of product were formed or incomplete conversion of the starting materials to the product was observed after 10 h at 80 °C. Excellent (100%) conversion to prop-2-enyl 3-phenylpropionate (**12**) took place with 1 and 2 mol % of $\text{HClO}_4\text{-SiO}_2$ after 6 h at 80 °C. No significant reduction in time was observed in increasing the catalyst loading to 2 mol % (Figure 1). Thus the effective/convenient catalyst loading was found to be 1 mol %.

To find out the best operative reaction temperature we considered the following sets of model reaction: condensation of (i) **1** (a representative arylalkyl carboxylic acid) with **2** (a representative high boiling alcohol), (ii) **10** with **11** (a representative acid sensitive alcohol), and (iii) benzoic acid **13** (a representative aryl carboxylic acid) with MeOH (a representative low-boiling alcohol). The reactions were performed under varying reaction temperature and time with 1 mol % of $\text{HClO}_4\text{-SiO}_2$ (Table 2). The optimum/best result was obtained at 80 °C.

We next planned to determine the influence of solvent on the catalytic efficiency of $\text{HClO}_4\text{-SiO}_2$ during the reaction of a equimolar ratio of **10** and **11**. The presence of solvent was found to have a detrimental impact on the yields of **12**. No esterification took place in DCM or hexane and dioxane afforded moderate yield (50%). However, better yields were observed when the reactions were performed with toluene (95%) and MeCN (80%) but the best yield (98%) was obtained under solvent-free conditions.

To extend the scope of the reaction as a general and practical procedure for esterification, we carried out the reaction of a series of aryl, heteroaryl, styryl, arylalkyl, aliphatic, and cycloalkane carboxylic acids with equimolar amounts of primary/secondary aliphatic, allylic, propargylic, benzylic, aryl alkyl, and cycloalkyl alcohols under solvent-free conditions at 80 °C in the presence of $\text{HClO}_4\text{-SiO}_2$ (1 mol %). The reactions were completed after 3–20 h affording excellent yields of the corresponding esters (Table 3). No competitive side reactions such as the rearrangement of unsaturated alcohols, decomposition of acid sensitive substrates, or decarboxylation of the carboxylic acids were observed. In the case of esterification with chiral alcohol, the enantiomerically pure ester was obtained in excellent yields without any racemization (entry 12). The esterification was performed with acid-sensitive carboxylic acids (entries 34–36) affording corresponding ester derivatives in high yields. The mildness/chemoselectivity of the

TABLE 2. Direct Esterification of **1** with **2**, **10** with **11**, and **13** with MeOH Catalyzed by $\text{HClO}_4\text{-SiO}_2$ under Varying Reaction Temperature^a

entry	acid	alcohol	temp (°C)	time (h)	yield (%) ^b
1	1	2	rt	24	nil ^c
2	1	2	60	24	44 ^c
3	1	2	80	3.5	98
4	1	2	100	3.5	99
5	1	2	100	2	74
6	10	11	rt	6	50 ^c
7	10	11	60	6	70 ^c
8	10	11	80	6	100
9	10	11	100	3.5	70
10	13	MeOH	rt	24	nil ^c
11	13	MeOH	60	24	62 ^c
12	13	MeOH	80	3	95
13	13	MeOH	80	2	80
14	13	MeOH	100	3	96
15	13	MeOH	100	2	79 ^c

^aThe acid (2.5 mmol) was treated with the alcohol (2.5 mmol) in the presence of $\text{HClO}_4\text{-SiO}_2$ (1 mol %) at the specified temperature (oil bath) for the specified time under solvent-free conditions until maximum/complete conversion (TLC/GCMS). ^bYield of the corresponding ester after purification. ^cThe unreacted starting materials remained unchanged.

$\text{HClO}_4\text{-SiO}_2$ catalyzed reaction was further demonstrated with *N*-*t*-Boc amino acid (entry 43) that resulted in the chemoselective formation of the corresponding ester in excellent yield without any effect on the *N*-*t*-Boc functionality. The reaction with proline (entries 37 and 38) further demonstrated the chemoselectivity as no competitive *N*-alkylation products were formed. The formation of the desired esters (entries 37, 38, and 43) in optically pure form (based on specific rotation) demonstrates the applicability of the methodology for chiral substrates. In most of the cases, the products obtained after the usual workup were pure (spectral data) and did not require additional efforts of purification. Wherever required, the purification was performed by column chromatography.

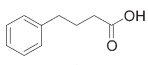



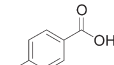




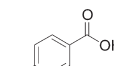

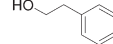

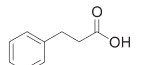



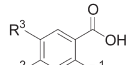












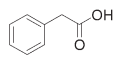






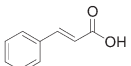












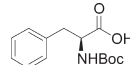



Keeping in view the wide industrial application of esterification for synthesis of drugs, drug intermediates, fine chemicals, and auxiliary agents like flavoring agents we planned to investigate the application of the catalyst system for syntheses of compounds used in industry.

Prodrugs are synthesized by converting the parent drug molecule to esters to improve solubility or bioavailability. Ibuprofen (**14**) is therapeutically used for its anti-inflammatory and analgesic action. However, it causes gastric irritation and if taken in higher doses for long periods of time can cause gastric ulcers. This side effect of the drug can be reduced if it is taken as a prodrug and the most effective prodrugs were the corresponding 2-propyl and *n*-butyl esters.²⁶ However, the syntheses of these prodrugs involved the traditional acid chloride strategy that generates acidic waste, requires elaborative purification, and affords moderate yields. The $\text{HClO}_4\text{-SiO}_2$ catalyzed direct esterification of **14** with *n*-butanol and 2-propanol afforded these prodrugs *n*-butyl and 2-propyl esters of ibuprofen **15** and **16** in 82% and 76% yields after 9 and 14 h, respectively (Scheme 3).

Fatty acid esters are used as emulsifiers or as oiling agents for foods and textiles, personal care emollients, surfactants

(26) (a) Bansal, A. K.; Khar, R. K.; Dubey, R.; Sharma, A. K. *Indian J. Exp. Biol.* **2001**, *39*, 280. (b) Bansal, A. K.; Khar, R. K.; Dubey, R.; Sharma, A. K. *Pharmazie* **1994**, *49*, 422.

TABLE 3. Direct Esterification of Various Carboxylic Acids with Different Alcohols Catalyzed by HClO₄-SiO₂^a

$(R)Ar-COOH + R^1-OH \xrightarrow[80\text{ }^\circ\text{C, Neat, 3-20 h}]{HClO_4-SiO_2 (1\text{ mol}\%)} (R)Ar-COOR^1$				$(R)Ar-COOH + R^1-OH \xrightarrow[80\text{ }^\circ\text{C, Neat, 3-20 h}]{HClO_4-SiO_2 (1\text{ mol}\%)} (R)Ar-COOR^1$					
entry	carboxylic acid	alcohol	time (h)	yield (%) ^{b,c}	entry	carboxylic acid	alcohol	time (h)	yield (%) ^{b,c}
1			4	93	24			20	95
2			6	84	25			7	95
3			3.5	94	26			8	90
4			5	98	27			16	72
5			5	90	28			16	80
6			6	92	29			14	78
7			7	87					
8			6	94	30	R ¹ = R ³ = H; R ² = NO ₂		16	79
9			4	92	31	R ¹ = F; R ² = H; R ³ = NO ₂		16	78
10			18	70	32			16	52
11			6	91	33			16	73
12			14	89	34			12	84
13			4	91	35			12	59
14			5	89	36			10	87
15			7	89	37			8	72 ^{d,e}
16			5	92	38		MeOH	5	80 ^{d,e}
17			7	89	39			8	84
18			6	92	40			8	90
19			9	92	41			6	95
20			10	84	42			7	92
21		MeOH	3	95	43			12	86 ^e
22			6	93					
23			5	90					

^aThe carboxylic acid (2.5 mmol) was treated with the alcohol (2.5 mmol) in the presence of HClO₄-SiO₂ (1 mol %) at 80 °C. ^bIsolated yield. ^cAll products were characterized by IR, ¹H/¹³C NMR, and EI-MS. ^dNo *N*-alkylated product was formed. ^eThe desired ester was obtained in optically pure form (based on optical rotation values).

and base materials for cosmetics, lubricants, and plastics. They are also used as solvents, cosolvents, and oil carriers in

the agricultural industry. The Fischer esterification of various long-chain fatty acids was carried out with long-chain alcohols

SCHEME 3. The HClO₄-SiO₂ Catalyzed Synthesis of Prodrugs of Ibuprofen

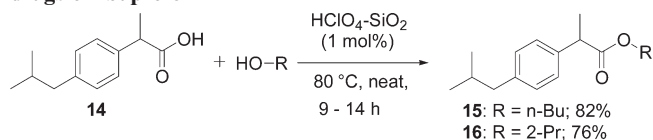


TABLE 4. Synthesis of Fatty Acid Esters by Direct Esterification of Long-Chain Aliphatic Carboxylic Acid with Long-Chain Alcohols Catalyzed by HClO₄-SiO₂^a

entry	product fatty acid ester	yield (%) ^{b,c}
1		95
2		92
3		90

^aThe carboxylic acid (2.5 mmol) was treated with the alcohol (2.5 mmol) in the presence of HClO₄-SiO₂ (1 mol %) at 80 °C for 10 h. ^bIsolated yield. ^cAll products were characterized by IR, ¹H/¹³C NMR, and EI-MS.

catalyzed by HClO₄-SiO₂ under solvent-free conditions affording the corresponding esters in excellent yields (Table 4).

Further, the HClO₄-SiO₂ catalyzed direct esterification procedure was found to be highly effective in the synthesis of various commercially used flavoring agents in excellent yields (Table 5).

To demonstrate the catalyst reuse, the esterification of stearic acid (2.85 g, 10 mmol) with stearyl alcohol (2.70 g, 10 mmol, 1 equiv) was performed at 80 °C for 10 h in the presence of HClO₄-SiO₂ (1 mol %) under solvent-free conditions. After the completion of the reaction (TLC), the reaction mixture was diluted with EtOAc and filtered through a plug of cotton. The cotton plug was washed with EtOAc (3 × 2 mL) and the combined filtrates were concentrated to isolate the product. The cotton plug retaining the catalyst was transferred to a round-bottomed flask (25 mL) and dried under rotary vacuum evaporation when the catalyst separated out from the cotton. The recovered catalyst was dried under vacuum (10 mmHg) at 80 °C for 24 h and reused for four consecutive fresh batches of reactions without significant decrease of its catalytic activity (Table 6).

For small/laboratory scale reaction (up to 50 mmol) where a small amount (up to 0.5 g) of the catalyst is required, the catalyst was preferably recovered by passing the reaction mixture through a cotton plug rather than classical filtration (using filter paper) to avoid loss of the catalyst due to possible adhering of some amount of the catalyst to the surface of the filter paper. We anticipated that the catalyst recovery following this process may not be convenient for industrial/large-scale preparation. Therefore the reaction of **13** (1 mol) with MeOH (1 mol) was carried out and after the completion of the reaction the catalyst was recovered by usual filtration (Table 7). The recovered catalyst was reused after drying repetitively for a fifth run (fourth recycle) and was found to retain its catalytic activity after which the recovered catalyst was observed to have a decrease in its activity as it required longer time (~10 h). An attempt to

TABLE 5. The HClO₄-SiO₂ Catalyzed Synthesis of Various Flavoring Agents^a

entry	flavour	flavouring agent (ester)	time (h)	yield (%) ^{b,c}
1	Citrus		7	90
2	Banana		12	86
3	Pineapple		8	92
4	Strawberry		12	88 ^d
5	Rose		8	92
6	Rose		6	94
7	Chocolate		11	83

^aThe carboxylic acid (3 mmol) was treated with the appropriate alcohol (3 mmol except for entry 4) in the presence of perchloric acid catalyst (1 mol %) at 80 °C. ^bIsolated yield. ^cAll products were characterized by IR, ¹H/¹³C NMR, and EI-MS. ^dThe reaction was carried out with the alcohol (MeOH) as the solvent.

TABLE 6. Reusability of HClO₄-SiO₂^a

entry	catalyst use	yield (%) ^{b,c}
1	fresh	92
2	1st recycle	92
3	2nd recycle	90
4	3rd recycle	83
5	4th recycle	80

^aThe mixture of stearic acid (10 mmol) and stearyl alcohol (10 mmol) was heated at 80 °C under solvent-free conditions for 10 h in the presence of HClO₄-SiO₂ (1 mol %). ^bIsolated yield of the ester. ^cThe product was characterized by IR, ¹H/¹³C NMR, and EI-MS.

reuse the catalyst simply by filtration and washing resulted in lower conversion to the product indicating that the solvent (used during washing) or the moisture (due to exposure) inactivates the catalyst probably by blocking/coordinating with the Brønsted acidic sites of the catalyst system.



To compare the advantage of the use of HClO₄-SiO₂ over the reported procedures, the esterification of **1**, **10**, *trans*-cinnamic acid **17**, **13**, cyclohexanecarboxylic acid **18**, and furan-2-carboxylic acid **19** with appropriate alcohols was considered as a few representative examples (Table 8). For the esterification involving long-chain aliphatic carboxylic acids and alcohols, esterification of palmitic acid **20** with stearyl alcohol **21** was considered. While in most of these cases better or comparative yields of the desired esters were obtained following the HClO₄-SiO₂ catalyzed procedure developed under this investigation, the reported procedures required stoichiometric amounts of additives,^{14d} special apparatus (reaction assembly),^{14a,c,d} solvent,^{14,15a} costly and moisture-sensitive catalysts,^{14a,d} corrosive/toxic reagents/catalyst,^{15,16} high temperature,^{14c} additional efforts of derivatization/activation of the carboxylic acid,^{15a} cumbersome workup, etc. These results clearly demonstrate that

TABLE 7. Reusability of HClO₄–SiO₂ for a Larger (1 mol) Scale Reaction of 13 with MeOH^a

entry	cat. use	scale ^b (mol)	amt of cat. used (g)	amt of cat. recovered (g)	time (h)	yield (%) ^{c,d}
1	fresh	1	20	19.8	3	95
2	1st recycle	0.5	10	9.6	3	94
3	2nd recycle	0.25	5	4.8	3.5	93
4	3rd recycle	0.1	2	1.9	3.5	89
5	4th recycle	0.05	1	0.9	4	88

^aThe equimolar mixture of 13 and MeOH was heated at 80 °C (oil bath) in the presence of HClO₄–SiO₂ (1 mol %). ^bIsolated yield of methyl benzoate. ^cThe product was characterized by IR, ¹H/¹³C NMR, and EI-MS.

TABLE 8. Comparison of the HClO₄–SiO₂ Catalyzed Direct Esterification with Reported Procedures with a Few Representative Common Substrates^a

entry	acid	alcohol (equiv)	cat (mol%)	conditions (apparatus, add/solv, temp, time, etc.)	yield (%) ^b
1	1		HfCl ₄ ·THF (0.2)	Dean-Stark, PhMe (solv), 120 °C, 5 h	94 ^c
2			HClO ₄ –SiO ₂ (1)	neat, 80 °C, 5 h	100
3	10		Zn(ClO ₄) ₂ ·xH ₂ O (10)	MgSO ₄ (1 equiv), Schlenk tube, 80 °C, 40 h	80 ^d
4			HClO ₄ –SiO ₂ (1)	neat, 80 °C, 14 h	89
5	13	2	Zn(ClO ₄) ₂ ·xH ₂ O (5)	MgSO ₄ (1 equiv), Schlenk tube, 100 °C, 2 6 h	89 ^d
6			HClO ₄ –SiO ₂ (1)	neat, 80 °C, 5 h	90
7	17	2	Zn(ClO ₄) ₂ ·xH ₂ O (5)	MgSO ₄ (1 equiv), Schlenk tube, 80 °C, 40 h	88 ^d
8			HClO ₄ –SiO ₂ (1)	neat, 80 °C, 6 h	92
9	18	2	Zn(ClO ₄) ₂ ·xH ₂ O (10)	MgSO ₄ (1 equiv), Schlenk tube, 80 °C, 40 h	70 ^d
10			HClO ₄ –SiO ₂ (1)	neat, 80 °C, 6 h	95
11	19	<i>n</i> -BuOH	4-DMAP (10)	TFFH (1 equiv), Et ₃ N (5 equiv), MeCN (solv), 80 °C, 15 h	97 ^e
12			HClO ₄ –SiO ₂ (1)	neat, 80 °C, 10 h	87
13	20	21	ZrOCl ₂ ·8H ₂ O (2)	Dean-Stark, mesitylene (solv), 162 °C, 24 h	85 ^f
14			HClO ₄ –SiO ₂ (1)	neat, 80 °C, 10 h	90

^aThe acid was treated with the alcohol in the presence of the catalyst under the specified conditions. ^bYield of the corresponding ester after purification. ^cReference 14a. ^dReference 14d. ^eReference 15a. ^fReference 14c.

HClO₄–SiO₂ is the best catalyst for direct esterification of carboxylic acids.

Conclusion

We have described herein HClO₄–SiO₂ as an extremely efficient reusable catalyst system for a general and practical esterification by direct condensation of carboxylic acids with alcohols in atom economical fashion. The advantages, such as (a) the use of a cheap and easy to handle catalyst, (b) solvent-free reaction conditions, (c) short reaction times, (d) high yields, (e) feasibility of large-scale operation, and (h) catalyst reuse, fulfill the “triple bottom line philosophy” of green chemistry.⁵

Experimental Section

Typical Procedure for the Preparation of Perchloric Acid Immobilized on Silica Gel (HClO₄–SiO₂). The catalyst system HClO₄–SiO₂ was prepared following the originally reported procedure.^{21a,c} To a suspension of silica gel (23.75 g, mesh no. 230–400) in Et₂O (50 mL) was added HClO₄ (1.25 g, 12.5 mmol, 1.78 mL of a 70% aq solution of HClO₄) and the mixture was stirred magnetically for 30 min at rt. The Et₂O was removed under reduced pressure (rotary evaporator) and the residue heated at 100 °C for 72 h under vacuum to afford HClO₄–SiO₂ (0.5 mmol g^{−1}) as a free-flowing powder.

Typical Procedure for the Synthesis of Ester by a Direct Condensation between a Carboxylic Acid and an Alcohol Catalyzed by HClO₄–SiO₂: *n*-Octyl 4-Phenylbutyrate (Table 2, Entry 3). The mixture of *n*-octanol (0.33 g, 2.5 mmol), 4-phenylbutyric acid (0.41 g, 2.5 mmol, 1 equiv), and HClO₄–SiO₂ (0.05 g, 1 mol %) in a round-bottomed flask (25 mL) was stirred magnetically at 80 °C until complete consumption of 4-phenylbutyric acid (3.5 h, TLC). The reaction mixture was diluted with EtOAc (25 mL) and filtered to remove the catalyst. The filtrate was washed with satd aq NaHCO₃ (2 × 5 mL) and water (5 mL), dried (MgSO₄), and concentrated under rotary vacuum evaporation to afford *n*-octyl 4-phenylbutyrate (0.65 g, 94%) as a clear oil. IR (Neat) ν 1739 cm^{−1}; ¹H NMR (CDCl₃, 300 MHz) δ 0.88 (t, *J* = 3.3 Hz, 3H), 1.28–1.43 (m, 10 H), 1.56–1.63 (m, 2 H), 1.90–2.02 (m, 2 H), 2.31 (t, *J* = 7.4 Hz, 2 H), 2.64 (t, *J* = 7.4 Hz, 2 H), 4.05 (t, *J* = 3.3 Hz, 2 H), 7.15–7.29 (m, 5 H); ¹³C NMR (CDCl₃, 75 MHz) δ 14.7, 23.2, 26.5, 27.2, 29.2, 29.8, 34.2, 35.7, 65.06, 126.5, 128.9, 129.1, 142.0, 174.1; MS (EI) *m/z* 276 (M⁺), identical with an authentic sample.^{14d} The cotton plug retaining the recovered catalyst was put in a round-bottomed flask (10 mL) and dried in a rotary evaporator whereupon the catalyst separated out from the cotton (45 mg, 90%). The catalyst was activated on heating under reduced pressure (10 mmHg) at 100 °C for 12 h and reused for four consecutive direct esterifications of 4-phenylbutyric acid (2.5 mmol), *n*-octanol (2.5 mmol), and HClO₄–SiO₂ (0.1 g, 0.05 mmol, 1 mol %) affording 92%, 90%, 83%, and 80% yields of *n*-octyl 4-phenylbutyrate after 4, 4, 5, and 5 h, respectively. The remaining reactions were carried out following this general procedure and in most cases the products obtained after the usual workup were pure (spectral data). Wherever required (isolated yield < 85%), the purification was performed by column chromatography (60–120 mesh silica gel, EtOAc:hexane). The spectral data (IR, NMR, and MS) of known

compounds were found to be identical with those reported in the literature. The spectral data (IR, NMR, and MS) of new compounds are provided below.

Typical Procedures for Large-Scale Synthesis of Esters by Direct Esterification of a Carboxylic Acid with an Alcohol Catalyzed by $\text{HClO}_4\text{-SiO}_2$ and Catalyst Recycle. **a. Reaction on a 50 mmol Scale and Catalyst Recovery by Using a Cotton Plug: *n*-Octyl 3-Phenylpropionate.** The mixture of *n*-octanol (6.50 g, 50 mmol), 3-phenylpropionic acid (7.50 g, 50 mmol, 1 equiv), and $\text{HClO}_4\text{-SiO}_2$ (1.0 g, 1 mol %) in a round-bottomed flask (50 mL) was stirred magnetically at 80 °C until complete consumption of 3-phenylpropionic acid (4 h, TLC). The reaction mixture was diluted with EtOAc (50 mL) and filtered to remove the catalyst. The filtrate was washed with satd aq NaHCO_3 (2×10 mL) and water (10 mL), dried (MgSO_4), and concentrated under rotary vacuum evaporation to afford the *n*-octyl 3-phenylpropionate (12.4 g, 95%) as clear oil. IR (Neat) ν 1736 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.88 (t, $J = 3.3$ Hz, 3 H), 1.27 (s, 10 H), 1.58 (t, $J = 3.3$ Hz, 2 H), 2.61 (t, $J = 7.8$ Hz, 2 H), 2.94 (t, $J = 7.8$ Hz, 2 H), 4.05 (t, $J = 3.3$ Hz, 2 H), 7.16–7.3 (m, 5 H); MS (EI) m/z 262 [M^+], identical with an authentic sample.²⁷ The cotton plug retaining the recovered catalyst was put in a round-bottomed flask (25 mL) and dried in a rotary evaporator whereupon the catalyst separated out from the cotton (0.48 g, 96%). The catalyst was activated on heating under reduced pressure (10 mmHg) at 100 °C for 12 h. The repetition of the reaction of 3-phenylpropionic acid (25 mmol) with *n*-octanol (25 mmol) in the presence of $\text{HClO}_4\text{-SiO}_2$ (0.5 g, 1 mol %) afforded the *n*-octyl 3-phenylpropionate (6.0 g; 93%) and the recovered catalyst (0.44 g, 90%) after the usual workup.

b. Reaction on a 1 mol Scale and Catalyst Recovery by Simple/Usual Filtration: Methyl Benzoate. The mixture of MeOH (32.04 g,

40.45 mL, 1 mol), benzoic acid (122.22 g, 1 mol, 1 equiv), and $\text{HClO}_4\text{-SiO}_2$ (20.0 g, 1 mol %) in a round-bottomed flask (500 mL) was stirred magnetically at 80 °C until complete consumption of benzoic acid (3 h, TLC). The reaction mixture was diluted with EtOAc (100 mL) and filtered through a filter paper to remove the catalyst. The filtrate was washed with satd aq NaHCO_3 (2×25 mL) and water (25 mL), dried (MgSO_4), and concentrated under rotary vacuum evaporation to afford the methyl benzoate (129.29 g, 95%) as a clear oil. IR (Neat) ν 1724 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 3.89 (s, 3H, COOCH_3), 7.39–7.43 (m, 2H, ArCH), 7.50–7.54 (m, 1H, ArCH), 8.02–8.8.04 (m, 2H, ArCH); MS (EI) m/z 136.2 [M^+], identical with an authentic sample.⁷ The filter paper retaining the catalyst was air-dried. The recovered catalyst (19.8 g) was placed on a beaker (100 mL) and treated at 100 °C for 12 h in a vacuum oven under reduced pressure (10 mmHg) to remove any moisture and volatile organic solvent that might block the catalytic sites. The recovered catalyst was used for four consecutive batches of reactions and on each occasion the recovered catalyst was used for the next batch. Thus, the repetition of the reaction of benzoic acid on 0.5, 0.25, 0.1, and 0.05 mol reactions with equimolar amounts of MeOH following this generalized procedure afforded the methyl benzoate in 94%, 93%, 89%, and 88%, respectively.

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Supporting Information Available: Typical experimental procedures, spectral data of all compounds, and scanned spectra of a few representative known and all unknown compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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