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Silica Sulfuric Acid as a Highly Efficient Catalyst for the Synthesis of Diarylacetic Acids

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Abstract

An efficient heterogeneous method for the synthesis of diarylacetic acids was developed utilizing silica sulfuric acid as a catalyst. The reaction is highly efficient with a small amount of catalyst for the combination of a variety of electron-neutral to electron-rich arenes with glyoxylic acid. The reaction can also be utilized to synthesize unsymmetric derivatives from activated mandelic acids in good to excellent yield.



INTRODUCTION

Much of the recent interest in the reaction design has been in the area of increasing efficiency and reducing waste, problems frequently solved through the use of heterogeneous catalysts. Heterogeneous solid catalysts, which offer simple separation from reaction mixtures, the potential for reusability, and often increased catalytic activity, afford many ideal properties for advancing synthetic chemistry.¹ While there are many different methods for the creation of these systems, a common strategy is the development of a solid-supported catalyst where the reactive species is covalently

attached or chemically adsorbed onto the surface of an inert material.² As the reaction takes place on the surface of the solid, maximizing the surface area of the support is crucial to maintaining sufficient reactivity.³ In addition, the solid support can provide a unique environment for a reaction to occur outside of the bulk solvent and even alter a reaction's outcome based on the specific properties of the surface.⁴ Silica gel, with its porous nature and polar properties, is one of the most commonly used solid supports, leading to development of a variety of new and interesting solid-phase acid catalysts.⁵

Silica sulfuric acid, formed from the adsorption of sulfuric acid onto the surface of dry silica gel, has received increased attention in recent years due to the convenient nature of the catalyst and the potential for reusability.⁶ The catalyst is non-corrosive, has low toxicity, and is not sensitive to moisture in the air.^{6a} Upon completion of a reaction, silica sulfuric acid can be isolated by a simple filtration, dried, and be reused effectively up to five times.⁷ In addition to serving as a proton source, the large and polar surface has been found to increase overall catalytic activity, allowing for much milder reaction conditions.⁶ This robust catalyst has been demonstrated to be an advantageous substitute for concentrated sulfuric acid for a variety of reactions, including additions,⁸ condensations,⁹ and heterocycle synthesis.¹⁰

 α, α -Diarylacetic acids are a diverse class of molecules that are important starting materials for a variety of biological compounds. Derivatives differing in the substituents on the aromatic rings have been shown to have a variety of interesting biological effects, exhibiting anti-inflammatory, analgesic, and antipyretic properties.¹¹ In addition,

diarylmoieties are commonly found in many commercial pharmaceutical agents, many of which utilize diarylacetic acid derivatives as starting materials in synthetic endeavors.¹² Due to the increased interest in diarylacetic acids and their derivatives, a cost-effective and facile synthesis of this class of molecules is essential.

A variety of methods have been explored for the synthesis of diarylacetic acids. Methods include the reduction of benzilic acids,¹³ carboxylation with carbon monoxide,¹⁴ and condensations of nucleophilic arenes.^{12b,15} The most efficient synthesis involves the condensation of two equivalents of a nucleophilic arene into a glyoxylic acid derivative with the use of a large excess of sulfuric acid.^{15a} Recent groups have improved on this procedure, reducing the amount of acid required by utilizing alternate acid sources.^{15e,f} Recently, Prakash and coworkers explored the use of triflic acid on a poly(4-vinylpyridine) solid support for the condensation of arenes with glyoxylic acid.^{15e} The reaction proceeded with excellent yields under mild conditions for a variety of alkyl and halogen substituted aromatic systems; however, no reports of more electron-rich oxygen bearing substrates were reported.

In line with our group's interest in the development of cleaner and more efficient reactions, we sought to develop an alternate and greener approach for the synthesis of diarylacetic acids utilizing a solid-supported catalyst system. Silica sulfuric acid emerged as an ideal candidate due to its high activity, low cost, and convenient removal. Silica sulfuric acid has proven useful in the synthesis of triarylmethanes from a related condensation of aldehydes with nucleophilic arenes in a related reaction,^{9d} but has yet to

be applied to the more electron-deficient carbonyl substrates required for diarylacetic acid derivatives. In this work, we report the use of silica sulfuric acid as a catalyst for the direct synthesis of diarylacetic acids by condensation of nucleophilic arenes with glyoxylic acid monohydrate.

DISCUSSION

Initial exploration of the use of silica sulfuric acid as the catalyst for the condensation of anisole with glyoxylic acid under neat conditions provided the desired product (**2a**) in moderate yield (Table 1). It was quickly determined that the lower yields were likely due to the insolubility of glyoxylic acid in anisole, which led to polymerization of the reagents and reduced activity of the catalysts. The addition of a small amount of a polar solvent significantly increases the yields by solubilizing the substrate intermediates, allowing for effective mixing during the reaction. Unfortunately, the use of water as a solvent proved unsuccessful, leading to the formation of a third phase in the already heterogeneous mixture and complicating the isolation of the products by filtration. Acetic acid was chosen as the ideal solvent due to convenience and cost. The reaction produces the highest yields with only a small amount of solvent, and increasing the solvent amount further does not significantly improve the yields.

The most commonly cited method for the synthesis of silica sulfuric acid involves the addition of chlorosulfonic acid to dry silica gel with removal of the resulting hydrogen chloride.^{9b} A more convenient method involves the addition of sulfuric acid to a suspension of silica gel followed by drying.^{10e} Both procedures produce a functional

catalyst for the condensation of arenes with glyoxylic acid, returning no significant difference in yields (Table 2). Even more surprising, silica sulfuric acid can be created *in situ* by the addition of silica gel and a small amount of concentrated sulfuric acid directly to the reaction mixture. The small amount of water present is readily adsorbed into the silica gel and does not have a significant effect on the reaction yield. This method remains a viable alternative to preforming the catalyst. The reaction was unsuccessful with just silica gel or sulfuric acid in similar concentrations to the solid-supported system, reinforcing the cooperative effect of the heterogeneous catalyst that has widely reported in other studies.^{2,3,6}

The reaction is general to a variety of electron-rich arenes, as shown in Table 3. Reaction yields are good to excellent, and most products are analytically pure following a simple acid/base extraction and precipitation. Only three equivalents of the reacting arene are required for the formation of the products, which is significantly lower than the large excesses often used in the homogeneous reaction.¹⁵ The reaction with active nucleophiles, such as substituted anisoles, are complete after four hours at 60 °C. More electron-poor arenes, such as xylene and toluene, require elevated temperatures (120 °C) to promote high yields, while the highly nucleophilic 1,3-dimethoxybenzene must be added at 0 °C and then warmed to room temperature to prevent unwanted side reactions. The products are generally formed a single regioisomer with addition occurring at the most nucleophilic position of the aromatic ring; however, substrates with equally activated positions, such as *o*-xylene and 3-methylanisole, produce the expected mixture of regioisomers with the double *para* addition preferred. The ratio of the regioisomers formed is similar to previously published methods.¹⁵ Sterically-hindered mesitylene proved to be a reasonable substrate for the reaction, providing the product **2m** in 82% yield. Benzene proved to be an unsuitable substrate, providing only a trace amount of the desired product (**2n**), though large amounts of polymerized products were observed. Increasing temperature or equivalents of benzene did not significantly improve the observed yield of diphenylacetic acid.

In an attempt to expand the scope of the reaction, we sought to explore a method to create differentially substituted diarylacetic acids. Mechanistically, α -aryl- α -hydroxyacetic acids (3) are a likely intermediate in the formation of diarylacetic acids from glyoxylic acid following the initial addition (Scheme 1). Therefore, 3 could be used as substrates for arylation under similar conditions to provide access to unsymmetric diarylacetic acids. The direct any lation of α -aryl- α -hydroxyacetic acids to diarylacetic acids has been reported, but typically utilizes stoichiometric amounts of strong Lewis acids, such as AlCl₃ or SnCl₄.¹⁶ Silica sulfuric acid has the potential to greatly expand the scope of this transformation, removing the requirement for anhydrous conditions. Gratifyingly, treatment of 2-(4-methoxyphenyl)acetic acid (3a) in the presence of anisole and silica sulfuric acid produced the desired diarylacetic acid 2a in an excellent 87% yield as a single regioisomer. As shown in Table 4, a variety of diaryl products can be formed from hydroxyacids in good to excellent yield utilizing silica sulfuric acid as a catalyst. Unsubstituted, electron-poor, or highly sterically hindered hydroxyacids, such as 2-(2methylphenyl)acetic acid (3c), do not undergo arylation, but instead cleanly produce acetate esters (6c) through reaction with the solvent. Stabilization of the developing

charge at the α -position is crucial for the reaction to occur. Without substantial stabilization through conjugation, either due to the lack of an appropriately strong activating substituents or the sterically induced twisting of the aromatic ring, the reaction cannot reasonably occur at the α -position. In this case, the previously reported Fisher esterification of alcohols occurs instead.¹⁷

In summary, we have expanded the utility of silica sulfuric acid catalysis of electrophilic aromatic substitution to include less electrophilic carbonyl substrates through the synthesis of diarylacetic acids from glyoxylic acid. This method serves as a compliment to recently reported green syntheses of these substrates, able to include increase regioselectivity and utilize electron-rich arenes. While the reuse of the catalyst in the current reaction has been explored, the activity of the recovered catalyst has been found to be significantly reduced. We are currently exploring alternative reaction and isolation conditions to improve reusability. Given the interesting properties of silica sulfuric acid, we hope to further explore its use in related acid-catalyzed reactions.

EXPERIMENTAL

All reagents and solvents are commercially available and were used directly with no further purification. The ¹H and ¹³C NMR spectra were recorded on 400- (100-) MHz Varian spectrometer and calibrated using residual undeuterated solvent (CDCl₃, δ H = 7.26 ppm, δ C = 77.16 ppm) as an internal reference. CDCl₃ was purchased from Cambridge Isotopes and used with no further purification. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Infrared (IR) spectra were recorded on a Perkin–Elmer 100 FT-IR spectrometer. Elemental analysis was performed by Galbraith Laboratories (Knoxville, TN, USA) using a CE-440 Elemental Analyzer. E. Merck silica gel (60, partical size 0.040–0.063 mm) was used for flash column chromatography. Silica sulfuric acid was prepared by the method of Zolfigol through the addition of chlorosulfonic acid to dry silica gel.^{9b}

General Procedure For The Reaction Of Glyoxylic Acid

Glyoxylic acid monohydrate (0.200 g, 2.2 mmol) and silica sulfuric acid (0.200 g, 1 mass equivalent) were suspended in acetic acid (1.0 mL) in a vial. The arene was then added dropwise at room temperature with vigorous stirring, and then the reaction mixture was heated to the appropriate temperature for the indicated time. Following cooling to room temperature, the mixture was diluted with ethyl acetate (20 mL), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified to analytical purity either by acid-base extraction or column chromatography.

General Procedure For The Reaction Of Hydroxyacetic Acids

Substituted mandelic acid (0.200 g) and silica sulfuric acid (0.200 g, 1 mass equivalent) were suspended in acetic acid (1.0 mL) in a vial. The arene (3 mole equivalents) was then added dropwise at room temperature with vigorous stirring, and then the reaction mixture was heated to the appropriate temperature for the indicated time. Following cooling to room temperature, the mixture was diluted with ethyl acetate (20 mL), filtered,

and the filtrate was concentrated *in vacuo*. The residue was purified to analytical purity either by acid-base extraction or column chromatography.

2,2-Bis(4-methoxyphenyl)acetic acid (2a): Using the standard procedures, glyoxylic acid monohydrate (0.200 g, 2.2 mmol) was reacted with anisole (0.70 mL, 6.5 mmol) at 60 °C for 4 hours. Following filtration to remove the catalyst and an acid-base extraction, **2a** (0.556 g, 94%) was isolated as an off-white solid. Spectral data is consistent with previously published reports.^{12b} ¹H NMR (400 MHz, CDCl3) δ = 7.22 (d, J = 9.1 Hz, 2H), 6.85 (d, J = 9.1 Hz, 2H), 4.93 (s, 1H), 3.77 (s, 6H) ppm; ¹³C NMR (100 MHz, CDCl3) δ = 178.1, 158.8, 130.4, 129.6, 114.0, 55.2, 55.2 ppm; IR (ATR) υ = 2971, 1699, 1610, 1584, 1457, 1440, 1305, 1218, 1174, 1113, 1027, 924, 812, 737 cm⁻¹; Anal. Calcd. for C₁₆H₁₆O₄: C, 70.58; H, 5.92. Found: C, 70.26; H, 6.20.

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SUPPORTING INFORMATION

Full experimental details and ¹H and ¹³C NMR spectra for all synthesized compounds can be found via the Supplementary Content section of this article's Web page.

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Table 1. Optimization of the silica sulfuric acid catalyzed synthesis of diarylacetic acids.

^a General conditions: glyoxylic acid monohydrate (0.20 g), anisole (3 equiv.), and silica sulfuric acid (0.20 g) were combined and heated to 60 °C for 4 hours. ^b Yield determined by ¹H NMR versus 1,3-dinitrobenzene as an internal standard. ^c Isolated yield.

Table 2. The effect of acid source on the synthesis of diarylacetic acids.



^a Yield determined by ¹H NMR versus 1,3-dinitrobenzene as an internal standard. ^b SSA prepared from chlorosulfonic acid.^{9b} ^c SSA prepared from concentrated sulfuric acid.^{10e}



Table 3. Synthesis of diarylacetic acids from glyoxylic acid.^a

^a General conditions: glyoxylic acid monohydrate (0.20 g), arene (3 equiv.), and silica sulfuric acid (0.20 g) were combined in acetic acid (1 mL) and heated to the indicated temperature for 4 hours. ^b Isolated as a 4:1 mixture of *para/para* addition and *para/ortho*

addition ^c Isolated as a 3:1 mixture of *para/para* addition and *para/ortho* addition. ^d Isolated as a 3.5:1 mixture of *para/para* addition and *para/ortho* addition.

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Table 4. Synthesis of diarylacetic acids from mandelic acid derivatives.^a

^a General conditions: mandelic acid (0.20 g), arene (3 equiv.), and silica sulfuric acid

(0.20 g) were combined in acetic acid (1 mL) and heated to 80 °C for four hours.^b

Isolated as a 4:1 mixture of para/para addition and para/ortho addition.







