Communication

Efficient Methyl Esterification Using Methoxyl Silica Gel as a Novel Dehydrating Reagent

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Methoxyl silica gel was prepared readily by the treatment of silica chloride with methanol. By using methoxyl silica gel as a dehydrating agent, carboxylic acids reacted with methanol in the presence of a protonic acid such as 12-phosphotungstic acid afforded the corresponding methyl esters in excellent yields.

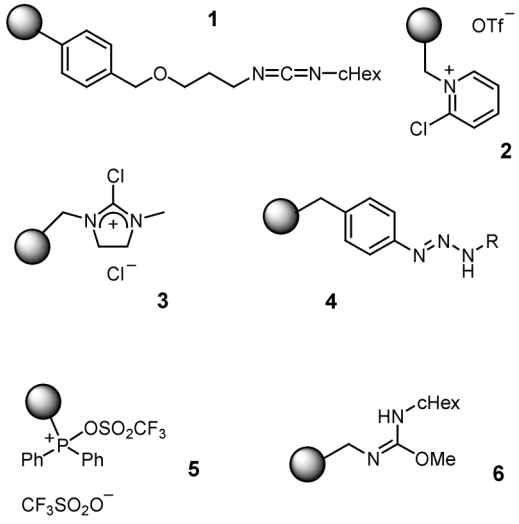
Keywords: Esterification; Equilibrium; Methoxyl silica gel; Dehydration.

INTRODUCTION

Esterification of carboxylic acids, especially direct esterification between carboxylic acids and alcohols, has wide academic as well as industrial applications.[1] It is considered to be one of the most important reactions in the field of synthetic organic chemistry as well as medicinal chemistry; hence, various condensation methods have been reported and are widely employed in the syntheses of natural and unnatural molecules that have carboxylic ester moieties.

Esterification from carboxylic acids is an equilibrium dependent reaction. In order for equilibrium reactions to proceed, the removal of water can be achieved in several ways. Firstly, by the physical removal of water using molecular sieves, however the dehydration efficiency of molecular sieves is relatively low. Another method involves azeotropic dehydration with an entrainer (e.g. toluene) using Dean and Stark apparatus; however, certain portion of products might be distilled off during this process. Alternatively chemical removal using a homogeneous dehydrating agents (coupling reagents), such as 1,3-dicyclohexylcarbodiimide (DCC), have been employed many years ago.[2] However, DCC and its analogues are often used in large excess to achieve optimal yields. The excess carbodiimides is then converted to dialkyl urea upon completion of the reaction, and thus one must isolate the desired esters from a large amount of the toxic dialkyl urea byproduct. To address these problems, various polymer-supported coupling reagents, for example, polymer bound carbodiimide (Scheme I, **1**),[3] Mukaiyama reagent (Scheme I, **2**),[4] PDMC (Scheme I, **3**),[5] triazenes (Scheme 1, **4**),[6] triphenylphosphine ditriflate (Scheme I, **5**),[7] and O-alkylisourea (Scheme I, **6**),[8] have been introduced in the literatures for the preparation of esters. Despite the utility of these reagents, development of simpler, more convenient, and inexpensive reagents is still desired.

Scheme I



Recently, silica chloride has been reported as a dehydrating reagent in the esterification of carboxylic,[9] phos-

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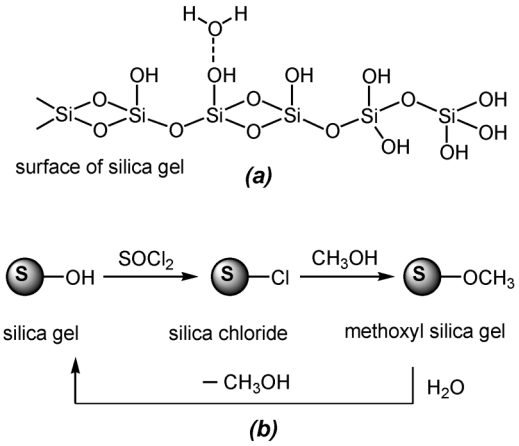
phonic, and phosphoric acids.[10] Silica chloride can be prepared from commonly used silica gel and thionyl chloride, so it is much cheap than above-mentioned polymer-supported coupling reagents. Unfortunately, it suffers from a significant problem, namely the generation of large amount of free hydrogen chloride gas during esterification. In our studies on the synthesis of methyl esters, we found that methoxyl silica gel (the reaction product of silica chloride and methanol) could be used as a dehydrating reagent in methyl esterification. To our knowledge, the use of alkoxyl silica gel as a reagent in organic synthesis has not been reported. The details and scope of this reaction strategy are presented herein.

RESULTS AND DISCUSSION

On the surface of silica gel some residual, uncondensed hydroxyl groups (silanol groups) from the original polymeric silicic acid remain. The silica surface is quite complex and contains more than one type of hydroxyl group; namely, single silanol group, geminal silanol groups, and three silanol groups (Scheme II, a).[11] These hydroxyl groups can be functionalized to afford specialty silica gels.

Scheme II



Silica chloride has been employed for a long time as the starting material of bonded stationary phase for chromatography. Generally, silica chloride was prepared by refluxing silica gel with thionyl chloride.[12] The unreacted $SOCl_2$ was distilled off and the resulting white or grayish powder was stored in the absence of moisture. Silica chloride reacts with anhydrous alcohols to afford alkoxy silica. However, the hydrolytic stability of alkoxy silica gel is much poor in comparison with organosilica derivatives bonded through carbon-silicon bonds. Therefore, alkoxy silica gel can play the role of water scavenger and generates the parent alcohol simultaneously (Scheme II, b).

In our investigation, methoxyl silica gel was prepared as a free-flowing white powder by treating silica chloride with anhydrous methanol. This procedure was successfully applied to prepare the methoxyl silica gel on a 20 g scale. The energy dispersive X-ray spectroscopy (EDX) analysis of the obtained methoxyl silica gel confirmed the presence of Si, O and C elements (Fig. 1). The loading of methoxyl was determined as 8 $mmol.g^{-1}$ by the weight loss after calcinated at 600 °C for 6 h. Methoxyl silica gel can be stored at room temperature in a desiccator with retention of its original activity.

To evaluate the potential of methoxyl silica gel as a coupling reagent, we initially examined its use for the synthesis of methyl 2-furoate. A comparison study was carried out between the methyl esterification of furoic acid with and without methoxyl silica gel under similar conditions. Typically, the mixture of furoic acid, a catalytic amount of 12-phosphotungstic acid (an eco- and user-friendly Brønsted acid) and methanol was stirred at reflux temperature. The reaction gives methyl 2-furoate in 80% yield of methyl 2-furoate after 12 h without the use of dehydrating reagent. Due to the equilibrium limitation, the yields fluctuated around 80% even though the reaction time was prolonged. This result is also in accord with that in a literature about direct methyl esterification (methyl 2-furoate, time: 10 h, yield: 80%, catalyst: concn. H_2SO_4).[13] The removal of water has the benefit of increasing the conversion for this

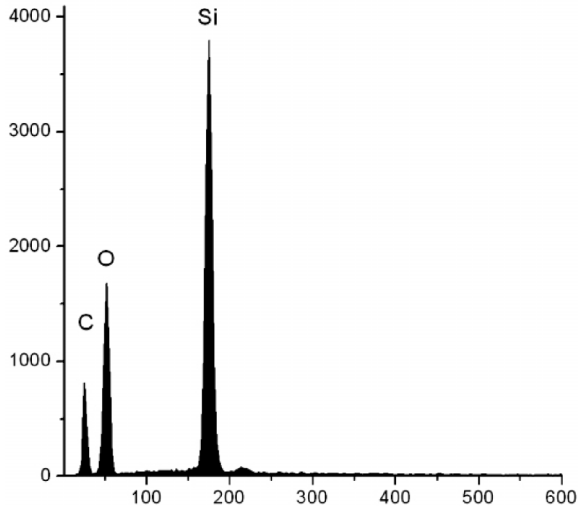
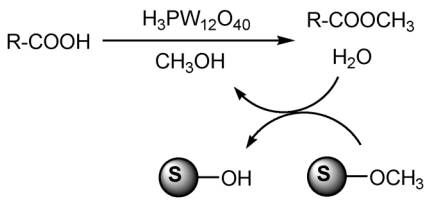


Fig. 1. EDX spectrum of methoxyl silica gel.

equilibrium limited reaction. To our delight, supra-equilibrium conversion was obtained in the presence of methoxyl silica gel as a dehydrating agent, and nearly quantitative isolated yield (98%) of desired ester was obtained within 4 h. These satisfactory results indicate the potential of methoxyl silica gel as a coupling reagent. Only 2 equiv. of methoxyl silica gel (based on total methoxyl groups) were necessary to ensure completed conversion of carboxylic acid.

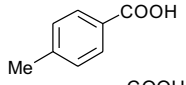
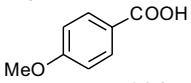
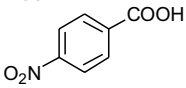
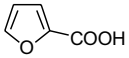
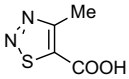
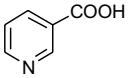
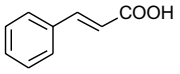
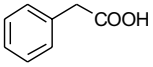
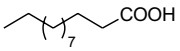
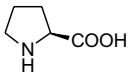
The methyl esterification of various carboxylic acids with methanol proceeded smoothly in the presence of 2 equiv. of methoxyl silica gel (Scheme III). The results are listed in Table 1. Apparently, the present method is quite general and found to be effective for aromatic, heterocyclic, open-chain conjugated and aliphatic carboxylic acids. Benzoic acids with either an electron-donating or an electron-withdrawing group gave the esters in good yield. 4-Methyl-1,2,3-thiadiazole-5-carboxylic acid (CAS: 18212-21-0), an intermediate of a plant fungicide TDL, yielded corresponding ester in 97% yield (Table 1, entry 5). Aliphatic carboxylic acids were equally effective for the esterification in comparison with aromatic ones. It has been reported that long-chain aliphatic acids, while also yielding pure esters in high yield, required much longer reaction times using coupling reagent anchored on polystyrene-based resin.[8b] This observation was attributed to the hydrophobic interactions with the resin which slow down the diffusion rates. In our experiments, no such a phenomenon was observed. Lauric acid gave corresponding ester in 98% yield within 1 h (Table 1, entry 9). Unprotected amino acids such as *L*-proline (Table 1, entry 10) could also be cleanly transformed into the corresponding amino esters. Logically saying, although we did not try in this work, this strategy might be employed in the reactions between carboxylic acids and certain alcohols (ROH) in the presence of corresponding alkoxy silica gel (SiO_2–OR).

Scheme III



Besides the esterifications starting from methanol, methyl esters may also be prepared by treatment of carboxylic acids with diazomethane, but this method is unsuitable for large scale reactions because of the toxicity and explosive nature of diazomethane. Hence, *in–situ* generated diazomethane from N-methyl-N-nitrosourea[14] or trimethylsilyl diazomethane[15] were developed as alternative reagents. The combination of LiOH and dimethyl sulfate (toxic) is another choice in the synthetic toolbox.[16] It has been mentioned in the introduction section that polymer-supported *O*-methylisourea reacts with carboxylic acids to afford methyl esters.[8] By all appearances, methoxyl silica gel has advantages over these reagents from the viewpoints of safety.

Table 1. Methyl esterification of various carboxylic acids

Entry	Substrates	Time (h)	Yield (%)
1		4	95
2		4	96
3		3	98
4		4	98
5		6	97
6		6	96
7		4	97
8		1	97
9		1	98
10		5	96

In reactions using polymer-supported coupling reagents, complete solvation of the polymer matrix is essential for the reactivity. The solvent must be chosen carefully in order to swell the resin. This allows reagents to penetrate into the core of the resin bead where the vast majority of the pendant functionalities are located. Silica gel has a rigid 3-D reticular structure so no swelling problem should be concerned by using our silica-based reagent. Moreover the silica gel employed has no cost when compared with the functionalized resin price.

In summary, methoxyl silica gel was shown to be a promising condensation reagent in the methyl esterifica-

tion of carboxylic acids. The key advantages of this method are the simplicity of work-up (simple filtration), ease and safety of reagent handling, cheapness of dehydrating reagent, and no organic byproducts which must be isolated from products after reactions. Today it is regularly used in our laboratory for the preparation of methyl esters and has proven to be efficient in parallel solution phase synthesis for the construction of combinatorial libraries. Investigations on the further application of methoxyl silica gel are currently in progress.

EXPERIMENTAL SECTION

Reagents and solvents are purchased from commercial resources expect 4-methyl-1,2,3-thiadiazole-5-carboxylic acid, which was prepared previously in our laboratory for pesticide research.[17] All products are known and gave spectral (^{1}H NMR and MS) data consistent with the assigned structures. ^{1}H NMR spectra were recorded on Bruker AV 400 spectrometer in $CDCl_3$ with TMS as internal standard. GC-MS data were recorded on a HP 6890-5973 apparatus.

Preparation of methoxyl silica gel

A stirred slurry of 20 g of well-dried fine powders of silica gel (G60, ~400 mesh) in $SOCl_2$ (25 mL) was refluxed for about 24 h in a flask charged with $CaCl_2$ drying tube. The excess $SOCl_2$ was removed by distillation. 20 mL of anhydrous methanol was then mixed with the obtained white powders and stirred at 0 °C for further 12 h. The solid was collected by filtration, washed thoroughly with anhydrous methanol, and dried under vacuum to afford methoxyl silica gel (26.6 g) as a free-flowing white powder. Methoxyl silica gel should be stored in a desiccator.

Methyl esterification using methoxyl silica gel as dehydrating reagent

To a suspension of methoxyl silica gel (2.5 g, 20 mmol of MeO) in 10 mL of methanol was added 10 mmol of carboxylic acid and 0.29 g (0.1 mmol) of $H_3PW_{12}O_{40}$. The reaction mixture was then stirred under refluxing for reaction times indicated in Table 1. On completion of the reaction as monitored by TLC, the resulting mixture was filtered and the excess methanol in filtrate was then removed by a rotary evaporator. The crude product was purified by column chromatography to afford the corresponding methyl ester.

Selected characterization data

Methyl 4-methyl-1,2,3-thiadiazole-5-carboxylate (Table 1, entry 5): Colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.93 (s, 3H, OCH_3), 2.95 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 162.43, 160.21, 138.99, 53.13, 13.90 ppm. GC-MS: 158 [M^+].

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