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Silica-supported perchloric acid as a recyclable catalyst for efficient trimethylsilyl cyanide addition to aldehydes†

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$HClO_4-SiO_2$ (0.6 mol%) acts as a highly effective catalyst for cyanation of various aldehydes to the corresponding *O*-trimethylsilyl cyanohydrins, in high yields and short reaction times. Copyright © 2007 John Wiley & Sons, Ltd.

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Introduction

The development of catalytic carbon–carbon bond-forming reactions leading to functionalized building blocks from simple starting matrials is a fundamental challenge in organic chemistry.[1] The Winkler reaction,[2] the addition of cyanide to carbonyl, which allows the preparation of cyanohydrin, is one of the oldest known carbon–carbon bond-forming reactions. Cyanohydrins are important intermediates in the realm of synthetic organic chemistry.[3,4] They have been used in Kiliani–Fischer synthesis of carbohydrates.[5] In addition, cyanohydrins are readily converted to useful functionalized compounds, such as α-hydroxyacids, α-hydroxyaldehydes, β-aminoalcohols and α-cyanoketones.[6] Furthermore, the hydroxyl group can be displaced by a wide range of nucleophiles to form functionalized nitriles.[7]

The classical Winkler reaction for the synthesis of cyanohydrins involves the treatment of carbonyl compounds with alkaline cyanides in aqueous medim. One of the initial drawbacks of this reaction is the use of highly toxic sodium cyanide and potasium cyanide. In order to avoid this inconvenience, the use of trimethylsilyl cyanide (TMSCN) has been introduced. TMSCN has been used as a safer and more efficient cyanide anion source compared with some of the cyanide reagents.[8] In this way, the aqueous medium can be changed to suitable organic solvents. The new protocols use acidic catalysts,[9] inorganic solid bases,[10] solubilized anionic species,[11] neutral metal compounds,[12] as well as diamino functionalized polymers[13] and inorganic/organic salts.[14] However, many of these methods involve the use of expensive reagents and extended reaction times, harsh conditions and an inert atmosphere, and also require tedious aqueous work-up, leading to the generation of a large amount of toxic waste. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. In order to overcome some of these problems, a new, safe and inexpensive catalytic procedure for the synthesis of cyanohydrin is highly desirable.

Owing to environmental and economic considerations of recent years, silica-supported catalysts have been found to be important for applications. Because of their larger surface area, they provide better selectivity, higher activities and better mechanical and thermal stabilities, and can easily be recovered from reaction mixtures and reused. As found recently, silica-supported perchloric acid has emerged as a poweful catalyst for various organic transformations, including synthesis of bis-indolylmethanes and bis-indolylglycoconjugates,[15] synthesis of 1,4-dihydropyridines,[16] synthesis of acylals from aldehydes,[17] transformation of thioglycosides to their corresponding 1-*O*-acetates,[18] 1,3-dithiolane/dithiane formation,[19] tetrahydropyranylation, oxathioacetalization and thioacetalization,[20] synthesis of coumarins via Pechmann condensation,[21] *N*-*tert*-butoxycarbonylation of amines,[22] selective removal of anomeric *O*-acetate groups in carbohydrates,[23] cleavage of benzylidene acetals,[24] glycosylation using sugar trichloroacetimidates as glycosyl donors,[25] selective deprotection of terminal isopropylidene acetals and trityl ethers,[26] Ferrier rearrangement of glycals,[27] acetal/ketal formation[28] and chemoselective carbon–sulfur bond formation.[29]

Herein we report our findings on the Winkler reaction using $HClO_4-SiO_2$ (0.6 mol%) to act as a highly effective catalyst.

Experimental

Preparation of the $HClO_4-SiO_2$ catalyst[30]

$HClO_4$ (1.0 g, 7 mmol, as a 70% aq. solution) was added to a suspension of SiO_2 (230–400 mesh, 11.35 g) in Et_2O (50 ml) while swirling. The mixture was concentrated and the residue was heated at 100 °C for 72 h under vacuum, while being magnetically stirred, to obtain $HClO_4-SiO_2$ (0.6 mmol/g) as a free-flowing powder (10 mg = 0.006 mmol of $HClO_4$).

Caution: although we did not have any accidents while using silica-supported perchloric acid, it is advisable to carry out all heating operations (evaporation, dring, etc.) in a fume hood using a suitable lab shield.

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Table 1. Synthesis of *O*-trimethylsilyl cyanohydrins **3a–k** in the presence of a catalytic amount of $HClO_4–SiO_2$ (0.6 mol%) at ambient temperature

Product	R	Time (min)	Yield[a] (%)
3a	*i*-Propyl	15	94[31]
3b	*tert*-Butyl	15	88[32]
3c	*n*-Pentyl	15	93[31]
3d	*n*-Hexyl	17	92[31]
3e	Phenyl	20	95(95, 95, 94)[b,32]
3f	4-Cl-Phenyl	30	90[32]
3g	4-Me-Phenyl	30	98[32]
3h	4-MeO-Phenyl	30	98[32]
3i	Benzyl	20	91[31]
3j	2-Furyl	20	96[31]
3k	Cinnamyl	20	96[32]

[a] Isolated yields.
[b] The yields of three subsequent runs using the same recovered catalyst.

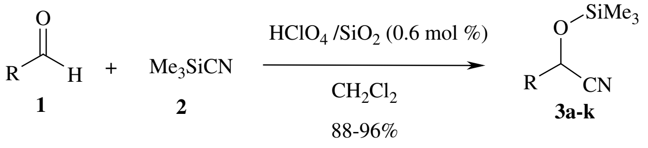
Typical experimental protocol

To a solution of the aldehyde (1.0 mmol) and trimethylsilyl cyanide (1.2 mmol) in CH_2Cl_2 (3 ml) was addedy $HClO_4–SiO_2$ (10 mg = 0.006 mmol of $HClO_4$, 0.6 mol%) and the reaction mixture was stirred at room temperature for an appropriate time (see Table 1). The reaction mixture was then filtered through a celite pad and concentrated to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane : ethylacetate, 1 : 1) to afford pure products. All isolated products gave satisfactory spectral (IR, ^1H NMR and ^{13}C NMR) data that were similar to those reported in the literature.[31,32]

Caution: the destruction of the catalyst does produce HCN. Therefore, all operations should be performed with special care and under a well-ventilated hood.

Results and Discussion

In continuation of these studies, we set out to explore the potential of $HClO_4–SiO_2$, an inexpensive catalyst, for the preparation of cyanohydrins through addition of TMSCN to aldehydes. In the first set of experiments, benzaldehyde was treated with TMSCN in CH_2Cl_2 by varying the quantity of catalyst at room temperature. After some experimentation, it was found that the use of 10 mg of $HClO_4–SiO_2$ catalyst (0.006 mmol of $HClO_4$) per 1.0 mmol of the benzaldehyde produced the corresponding *O*-trimethylsilyl cyanohydrin in excellent yield within 20 min at room temperature. Using the same conditions, a series of *O*-trimethylsilylated cyanohydrins were prepared in excellent yield at room temperature using aldehydes and trimethylsilyl cyanide (Scheme 1).



Scheme 1.

In most cases clean formation of products was observed. However, for the preparation of analytical samples of products, the crude reaction mixture was passed through a short pad of silica gel using hexane–ethyl acetate (1 : 1) as the eluant. The insolubility of the catalyst in different organic solvents provides an ease of seperation of the catalyst and the product. The catalyst was easily seperated by simple filtration and the recovered $HClO_4–SiO_2$ was reused in subsequent reactions without significant decrease in activity even after three runs. For example, the reaction of benzaldehyde (**1e**) and TMSCN (**2**) afforded the corresponding *O*-trimethylsilylated cyanohydrin (**3e**) at 95, 95 and 94% over three cycles. (Table 1)

This method seems to be a general synthetic route to cyanosilylation of aldehydes. Unfortunately, ketones are not amenable to the cyanation condition. Additionally, we found that cyanation of an aldehyde rather than a ketone was performed in more than 99% selectivity. The reaction of isobutyraldehyde and acetophenone with TMSCN in the presence of $HClO_4–SiO_2$ (0.6 mol%) gave *O*-trimethylsilylated cyanohydrin (**3a**, 94%) and unreacted acetophenone, respectively.

Conclusion

In summary, this new protocol represents a safer, simpler and more environmentally friendly alternative to the classical Winkler conditions, avoiding the use of expensive and toxic Lewis acids and therefore permitting the use of substrates sensitive to Lewis acid conditions. There are several advantages in the use of $HClO_4–SiO_2$ as catalyst for this transformation, which include high yields of products, simplicity in operation and cleaner reaction profiles. The purification of products after the usual work-up was in most cases unnecessary.

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