

MAGNETICALLY RECOVERABLE BASE AND ACID CATALYSTS IN ONE-POT SEQUENTIAL REACTIONS WITHOUT MUTUAL DESTRUCTION

Received 22 August 2009

PHAN THANH SON NAM¹, CHRISTOPHER W. JONES²

¹Ho Chi Minh City University of Technology, Viet Nam

²Georgia Institute of Technology, Atlanta, USA

ABSTRACT

A convenient approach for carrying out different reactions requiring acid and base catalysts in one pot with recovery of each individual catalyst in its essentially pure form was demonstrated. Separation of the base CoFe_2O_4 magnetic nanoparticles (MNP) catalyst from the solid catalyst mixture has proved to strongly depend on the nature of the solid acid catalyst. Combining the base MNP catalyst that was magnetically recoverable with a cation exchange resin catalyst that was recovered gravimetrically, one-pot deacetalization-Knoevenagel reactions and one-pot aldehyde protection-deprotection readily proceeded with 100% conversions being achieved under very mild conditions.

I - INTRODUCTION

The vast majority of chemical syntheses have been conducted using the traditional paradigm of single catalytic reactions with homogeneous or heterogeneous chemical catalysts, followed by costly catalyst and/or product purification steps. In recent years, multi-step reactions carried out in a single reactor without complex reactor design or specific purification procedures have attracted considerable attention [1]. A primary reason is that controlling one-pot, multi-step reactions using traditional homogeneous catalysts is rather difficult since, unlike for biocatalysts, interactions between soluble catalysts can cause deactivation [2]. To overcome this problem, several attractive methods, for example, anchoring active sites onto polymers [3], and doping of reactive species into sol-gel materials [4] have been developed. However, in such cases, after reaction, catalysts were isolated in

the form of a solid mixture.

We recently reported the utilization of diamine-functionalized superparamagnetic spinel ferrite (CoFe_2O_4) nanoparticles as efficient heterogeneous catalyst for low temperature liquid phase reactions such as the Knoevenagel and cyanosilylation transformations under very mild conditions [5, 6]. The base superparamagnetic nanoparticles catalyst could be facilely isolated from the reaction mixture by simple magnetic decantation using a permanent magnet. In this paper, we wish to report a convenient approach for carrying out different reactions requiring acid and base catalysts in one pot with recovery of each individual catalyst in its essentially pure form. This concept was demonstrated by combining a base catalyst that was magnetically recoverable with an acid catalyst that was recovered gravimetrically in different sequential reactions.

II - EXPERIMENTAL

1. Materials and instrumentation

Chemicals were purchased from Aldrich, Alfa Aesar, and Acros and used as received without further purification. Amberlyst cation exchange resin (Aldrich, 16-50 mesh) was washed with copious amounts of THF and toluene, and dried under vacuum overnight at room temperature. The CoFe_2O_4 magnetic nanoparticles were synthesized, functionalized with *N*-[3-(trimethoxysilyl)propyl]-ethylenediamine and characterized using X-ray powder diffraction (XRD), transmission electron microscope (TEM) and Fourier transform infrared (FT-IR) as previously reported [5, 6]. Sulfonic acid-functionalized SBA-15 silica was prepared using a two-step procedure and characterized using X-ray powder diffraction (XRD), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) as previously reported [7]. A Fischer Scientific FS60H was used to sonicate samples.

Gas chromatographic (GC) analyses were performed using a Shimadzu GC 14-A equipped with a flame ionization detector (FID) and an HP-5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). The temperature program for GC analysis heated samples from 50 to 140°C at 30°C/min, from 140 to 300°C at 40°C/min, and held at 300°C for 2 min. *p*-Xylene was used as an internal standard to calculate reaction conversion. GC-MS analyses were performed using a Hewlett Packard GC-MS 5890 with a DB-5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). The temperature program heated samples from 30 to 300°C at 15°C/min and held at 300°C for 5 min. Elemental analyses were performed by Desert Analytics Lab (Tucson, Az, USA) with inductively coupled plasma - mass spectrometry (ICP-MS).

2. One-pot deacetalization-Knoevenagel reactions

Base magnetic nanoparticles (8 mg), cation exchange resin (50 mg), toluene (4 ml), benzaldehyde dimethylacetal (15.2 mg, 0.1 mmol), malononitrile (13.8 mg, 0.2 mmol), and *p*-xylene (10.6 mg, 0.1 mmol) were placed into a 10 mL glass vessel. The mixture was stirred at room temperature under an argon atmosphere. Reaction conversion was monitored by withdrawing aliquots from the reaction mixture at different time intervals, quenching with acetone, filtering through a short silica gel pad, analyzing by GC with reference to *p*-xylene, and further confirming by GC-MS.

2. Catalyst separation

Separation of catalysts was achieved by sonicating the reaction vessel after applying an external permanent magnet to one side of the vessel. After quantitative conversion of the one-pot reaction was achieved, an external magnetic field was applied on the outer surface of the glass reaction vessel containing the magnetic nanoparticles and the resin catalyst. The system was sonicated at room temperature to facilitate the separation of one catalyst from the other. The non-magnetic resin catalyst was removed from the reaction vessel by decantation while the external magnet held the basic nanoparticles stationary inside the vessel. The separated resin catalyst was then added to toluene, sonicated to remove any physisorbed magnetic nanoparticles, and separated by magnetic decantation.

III - RESULTS AND DISCUSSION

Deacetalization is an important acid-catalyzed reaction in organic synthesis, forming carbonyl compounds that are often further reacted to the target products using base catalysts. In this research, one-pot synthesis of benzylidene malononitrile from malononitrile and benzaldehyde dimethylacetal was initially demonstrated using the sulfonic acid-functionalized SBA-15 silica as the acid catalyst for the first reaction (deacetalization) and the amino-functionalized CoFe_2O_4 magnetic nanoparticles (MNP) as the base catalyst for the

second reaction (Knoevenagel) (figure 1). Both catalysts and all the reagents were added to a single reaction vessel at time zero. The acid and the base catalysts used in the sequential reactions were prepared and characterized as previously reported [5-7]. SBA-15 is known to be a well-defined, hexagonal mesoporous silica material with straight mesopores that are

connected through small micropores [8]. Sulfonic acid-functionalized silica was previously used as catalysts in several organic transformations [7, 9]. Amino-functionalized CoFe_2O_4 MNP previously exhibited high activity in the Knoevenagel and cyanosilylation reactions [5, 6].

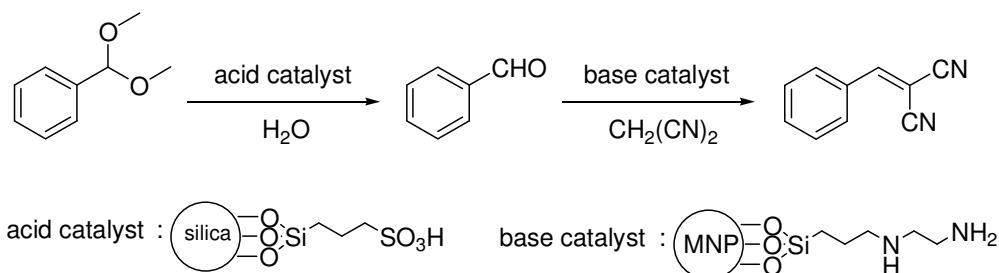


Figure 1: One-pot sequential deacetalization-Knoevenagel reactions using the acid silica catalyst and the base MNP catalyst

It was observed that the deacetalization reaction of benzaldehyde dimethylacetal to form benzaldehyde, and the Knoevenagel reaction of benzaldehyde with malononitrile to form benzylidene malononitrile directly proceeded in the presence of *both* the sulfonic acid-functionalized silica catalyst and the MNP catalyst. Using 2 mol% acid and 2 mol% base solid catalysts in toluene, 100% conversion of benzaldehyde dimethylacetal was achieved within 10 minutes, and 100% conversion of benzaldehyde was obtained within 40 minutes (figure 2). In the absence of the MNP catalyst, benzaldehyde became the only product, while no reaction occurred without the solid acid catalyst. When either the MNP catalyst or the solid acid catalyst was replaced by a homogeneous reagent, such as *N*-propylethylenediamine and *p*-toluenesulfonic acid respectively, no reaction occurred. The results indicated that the reaction between a solid base and a solid acid scarcely occurred, while a homogeneous acid could readily neutralize a solid base, and *vice versa*.

Furthermore, the addition of water to the reaction mixture was not necessary because trace of water in toluene initiated the deacetalization reaction, and subsequently the successive Knoevenagel reaction produced enough water for the first reaction. Today, deacetalization reactions are normally carried out in aqueous organic media, resulting in costly catalyst and/or product purification steps [10]. It should also be noted that consecutive reactions in one pot are possible, naturally in homogeneous systems as well, but with a disadvantage over the heterogeneous procedure we demonstrate herein: in a homogeneous system, after the first reagent or catalyst has completed its task, the second reagent or catalyst has to be added in excess to destroy the first and activate the next step. This results in the used catalysts simply becoming a component of the reaction waste. Therefore, the sequential one-pot reaction system described herein might contribute significantly to the promotion of simple, efficient, and greener processes.

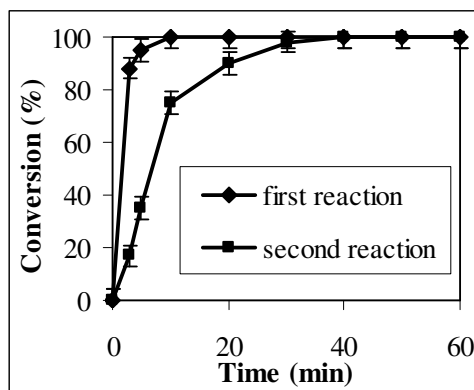


Figure 2: One-pot deacetalization-Knoevenagel reactions using the base MNP and sulfonic acid-functionalized SBA-15 silica catalysts

Several attractive methods have been developed to successfully perform multi-step reactions in a single reactor using simultaneously solid acid and solid base catalysts. However, after the reaction, it is impossible to separate the solid acid from the solid base. The base MNP catalyst, theoretically, might be isolated from the solid mixture by magnetic decantation using a permanent magnet, while the non-magnetic catalyst could be isolated gravimetrically. Unfortunately, experimental results showed that all efforts to separate the base MNP catalyst from the acid mesoporous SBA-15 silica one after the one-pot sequential deacetalization-Knoevenagel reaction were unsuccessful. This could be rationalized based on the strong physisorption of the nanoparticles on the high-surface-area SBA-15 silica catalyst ($960 \text{ m}^2/\text{g}$).

It was therefore decided to use other type of solid acid catalyst to avoid the physisorption of the nanoparticles on the surface of the support, facilitating the separation of one catalyst from the other. After screening several solid supports, Amberlyst cation exchange resin (particle size: 0.60-0.85 mm, surface area: $53 \text{ m}^2/\text{g}$), a sulfonic acid polymeric resin based on crosslinked styrene divinylbenzene copolymer was employed as the solid acid catalyst for the one-pot system. Indeed, Amberlyst cation exchange resin previously exhibited high activity in several acid-catalyzed organic transformations [10, 11]. It was also observed that combining the base MNP and the cation exchange resin catalysts, the one-pot deacetalization-Knoevenagel reactions readily proceeded with 100% conversions of both reactions being achieved (figure 3).

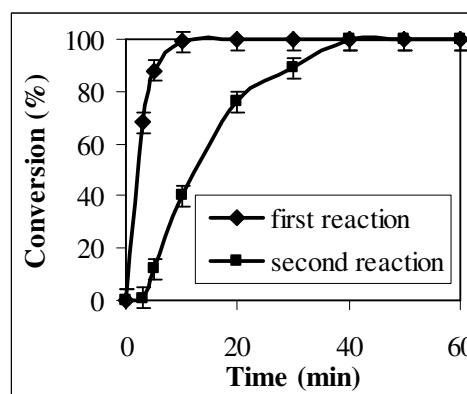


Figure 3: One-pot deacetalization-Knoevenagel reactions using the base MNP and cation exchange resin catalysts

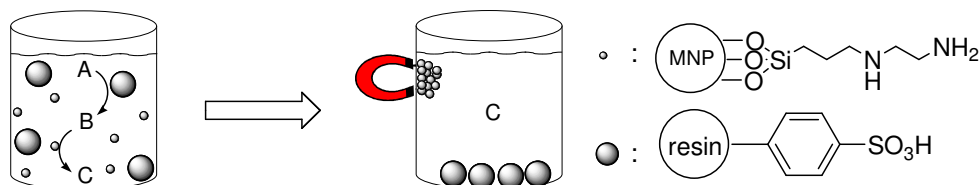


Figure 4: Schematic description of one-pot sequential reactions with recovery of each individual catalyst in its pure form

After the one-pot reaction, the two catalysts were separated by sonicating the reaction vessel and affixing a small permanent magnet externally to one wall of the vessel (Figure 4). The non-magnetic resin catalyst was removed from the reaction vessel by decantation while the magnet held the base MNP catalyst stationary in the vessel. It was observed that each catalyst was recovered in essentially pure form, as indicated by elemental analysis (ICP-MS) of the recovered catalysts with reference to the corresponding fresh catalysts. The amount of sulfur, an elemental tag for the resin catalyst, detected in the magnetic nanoparticle catalyst before and after reaction was essentially identical within experimental errors (magnetic base catalysts = 0.07% S before reaction and 0.05% after reaction). The same is true of the amount of iron, an elemental tag for the magnetic catalyst, in the resin catalyst before and after reaction (resin acid catalyst = 0.01% Fe before reaction and 0.03% after reaction). The fact that each catalyst could be recovered in

essentially pure form therefore exhibited advantages over other methods described in the literature.

The study was then extended to other type of one-pot sequential reactions. *O*- and *N*-protection is often necessary in organic synthesis. Considerable attention has been paid to the design of effective protecting groups for a variety of functionalities [12]. Normally, 1,2-diols and 1,3-diols are used to protect the carbonyl group of aldehydes and ketones. A homogeneous acid such as HCl is subsequently employed to deprotect the groups, increasing the reaction waste. We herein demonstrate a new strategy for the protection-deprotection of the carbonyl group in one pot using the base MNP for the protection step in conjunction with the cation exchange resin for the deprotection step. Trimethylsilyl cyanide was used as protecting agent, transforming the aldehyde group into its corresponding cyanohydrin trimethylsilyl ether (figure 5).

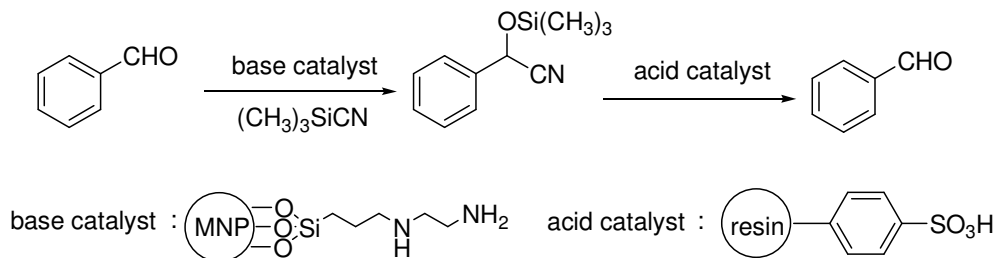


Figure 5: One-pot protection-deprotection using the base MNP and cation exchange resin catalysts

At time zero, the base MNP catalyst and trimethylsilyl cyanide were added to convert benzaldehyde into its corresponding cyanohydrin trimethylsilyl ether. It was observed that 100% conversion of benzaldehyde was achieved within 5 minutes using 2 mol% MNP catalyst. The cation exchange resin catalyst was subsequently introduced to the reaction vessel to deprotect the aldehyde group without separating the base nanoparticles. 100% conversion of cyanohydrin trimethylsilyl ether

back to benzaldehyde was achieved within 60 minutes. As with the one-pot deacetalization-Knoevenagel reactions, after the protection-deprotection sequences, the base MNP catalyst could be magnetically separated and the cation exchange resin catalyst could be recovered gravimetrically. The protection-deprotection approach demonstrated herein therefore offers advantages over traditional methods. However, further investigation on the topic is needed.

IV - CONCLUSIONS

In conclusion, we have demonstrated a convenient approach for performing different reactions requiring acid and base catalysts in one pot with recovery of each individual catalyst in its essentially pure form. Combining the base MNP catalyst that was magnetically recoverable with a cation exchange resin catalyst that was recovered gravimetrically, one-pot deacetalization-Knoevenagel reactions and one-pot aldehyde protection-deprotection readily proceeded with 100% conversions being achieved under very mild conditions. However, separation of the base MNP catalyst from the catalyst mixture has proved to strongly depend on the nature of the solid acid catalyst, and the problem still needs further study. The one-pot reaction system described herein might contribute significantly to the promotion of simple, efficient, and greener processes. Further exploration and optimization of using the MNP catalyst in conjunction with other catalysts in one pot appears warranted, and is the focus of on-going investigation.

REFERENCES

1. L. Veum, U. Hanefeld. *Chem. Commun.*, 825 (2006).
2. B. Voit. *Angew. Chem. Int. Ed.* **45**, 4238(2006).
3. B. Helms, S. J. Guillaudeu, Y. Xie, M. McMurdo, C. J. Hawker, J. M. J. Frechet. *Angew. Chem. Int. Ed.* **44**, 6384 (2005).
4. F. Gelman, J. Blum, D. Avnir. *J. Am. Chem. Soc.* **124**, 14460 (2002).
5. N. T. S. Phan, C. W. Jones. *J. Mol. Catal. A.* **253**, 123 (2006).
6. N. T. S. Phan, C. W. Jones. *J. Chem.* in press (2007).
7. B. C. Wilson, C. W. Jones. *Macromolecules*, **37**, 9709 (2004).
8. D. Zhao, Q. Huo, J. Feng, B. F. Chmelka, G. D. Stucky. *J. Am. Chem. Soc.* **120**, 6024 (1998).
9. S. Shylesh, Prinson P. Samuel, Ch. Srilakshmi, Renu Parischa and A. P. Singh. *J. Mol. Catal. A.* **274**, 153 (2007).
10. K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda. *J. Am. Chem. Soc.* **127**, 9674 (2005).
11. J. W. Yoon, J. S. Chang, H. D. Lee, T. J. Kim, S. H. Jung. *J. Mol. Catal. A.* **260**, 181 (2006).
12. Elisa Danieli, Jérôme Lalot and Paul V. Murphy. *Tetrahedron*, **63**, 6827 (2007).

Corresponding author: Phan Thanh Son Nam

Ho Chi Minh City University of Technology, Viet Nam
268 Ly ThuongKiet Str, 10 District, Ho Chi Minh City
Email: ptsnam@hcmut.edu.vn or ptsnam@yahoo.com.