Received: 12 April 2008 Revised: 17 May 2008 Accepted: 19 June 2008

(www.interscience.com) DOI 10.1002/aoc.1442

Superparamagnetic iron oxide as an efficient and recoverable catalyst for rapid and selective trimethylsilyl protection of hydroxyl groups

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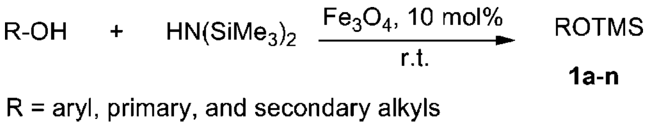
At room temperature and under solvent-free conditions, various types of alcohols and phenols were efficiently protected within a few minutes using hexamethyldisilazane and magnetically recoverable Fe_3O_4. Preferential protection of primary alcohols was observed when they competed with secondary or tertiary alcohols. Highly selective protection of phenols in the presence of aromatic amines or thiophenol was also observed.

Keywords: superparamagnetic Fe_3O_4; HMDS; silyl ethers; solvent-free; alcohols

Introduction

Lewis acid-catalyzed reactions constitute one of the most useful means in modern organic synthesis of allowing smooth interchange of an array of different functional groups.[1–3] There are, however, drawbacks associated with the use of a conventional homogeneous Lewis acid such as the additional work-up step required for destruction of the catalyst. This usually ends up with complete decomposition of the Lewis acid and therefore makes its reuse impossible. In addition, the resulting inorganic salts dissolve in the aqueous phase and usually produce environmentally non-tolerable waste. To overcome these limitations, heterogeneous catalytic systems have been extensively used in recent years in various synthetic transformations.[4–8] Mild reaction conditions, straightforward experimental procedures, minimal waste disposal and reusability of catalysts are the advantages of heterogeneous systems. In this context, magnetic particles have emerged as one the most useful heterogeneous catalysts due to their numerous applications in nanocatalysis,[9] biotechnology,[10,11] and medicine.[12,13] Additionally, the magnetic property of such particles provides the opportunity for quantitative recovery of the catalyst by the use of an external magnetic field.[14]

Protection of hydroxyl groups is a common practice in synthetic organic[15] and analytical chemistry.[16,17] Many multi-step syntheses and chemical transformations involve at least one step of hydroxyl group protection.[18,19] Conversion of alcohols into their corresponding silyl ethers is perhaps the most popular strategy for this purpose.[20] In this context, 1,1,1,3,3,3-hexamethyldisilazane (HMDS) has emerged as the most versatile reagent in recent years for trimethylsilyl (TMS) protection of alcohols and phenols. Commercial availability, ease of handling, use of mild conditions, formation of ammonia as the only by-product,[21] and convenient work-up are among the advantages of HMDS over traditional silyl chloride or triflate reagents.[22] However, the poor silylation power is the main drawback for application of HMDS.[23] This limitation dictates the use of harsher reaction conditions and longer time periods. Several catalytic systems have been developed to ease HMDS silylation processes by using extra additives,[24–26] microwave irradiation,[27] solid phase synthesis,[28–30] ultrasound activation,[31] ionic liquid mediation[32] and Lewis acid catalysis.[33–41] Although these methods improve the reaction conditions, there are still demands for environmentally friendly procedures promoted by fully recoverable heterogeneous catalysts. In the present article, we communicate the use of recoverable superparamagnetic iron oxide (Fe_3O_4) particles for room-temperature TMS protection of alcohols and phenols within short time periods (Scheme 1). Reactions proceed with the use of no solvent or additive and recovery of the catalyst is easily achieved with a permanent magnet.



Scheme 1. Fe_3O_4 catalyzed TMS protection of alcohols and phenols.

Experimental

General

Reactions were monitored by thin-layer chromatography (TLC) and gas chromatography (GC). TLC experiments were carried out on ready-to-use silica gel-coated aluminum plates from Aldrich with UV indicator, and compounds were visualized by UV fluorescence or by staining with Jones solution. Ethyl acetate–hexane (1 : 6) solution was used as eluent. Distillations were performed using a bulb-to-bulb distillation unit (Büchi 6KR-51). Chemicals were purchased from Merck and Aldrich and were used as received. Fe_3O_4 was prepared according to available procedures.[42]

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Analyses

Infrared spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions were reported as wave numbers (cm^{-1}). All ^{1}H-NMR spectra were performed in $CDCl_3$ and recorded on a Bruker AC 80 MHz instrument using tetramethylsilane as the internal standard and the chemical shifts were expressed as δ units. ^{1}H-NMR spectra were collected at 80 MHz. The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, t = triplet, m = multiplet. Mass spectra were recorded on a Finnigan Mat 8430 apparatus at ionization potential of 70 eV. GC analyses were performed using a Varian CP-3800 instrument with column type of WCOT Fused Silica (15 m) and VF-1ms stationary phase.

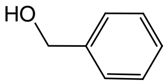
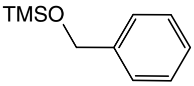
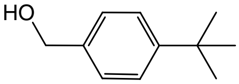
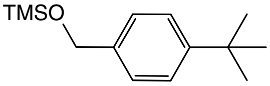
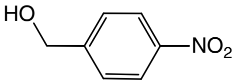
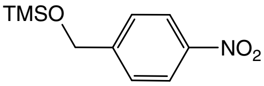
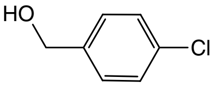
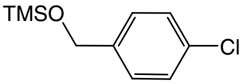
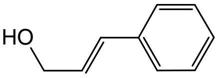
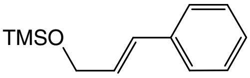
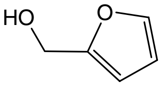
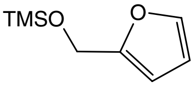
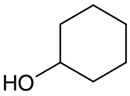
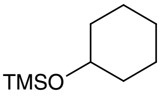
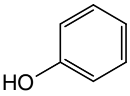
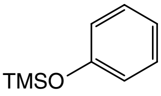
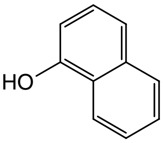
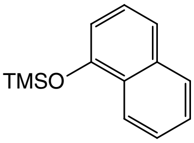
Typical procedure for the preparation of trimethylsilylethers

A solvent-free mixture of an alcohol (5 mmol), HMDS (5 mmol), and Fe_3O_4 (0.5 mmol; 10 mol%) was shaken (800 rpm) in a test tube at ambient temperature for an appropriate length of time (Table 1). The course of the reaction was monitored by TLC or GC until complete consumption of the starting materials was observed. After reactions reached completion, a permanent magnet was externally applied to the outside wall of the reaction tube to separate the solid catalyst from the solution portion. Products were obtained by evaporation of the volatile portion under reduced pressure and were purified with a bulb-to-bulb distillation unit, when necessary. The identity of the products was confirmed by the comparison of their spectroscopic data with those of compounds available in the literature.

General procedure for competitive trimethylsilylation reactions

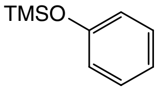
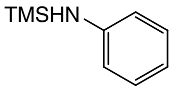
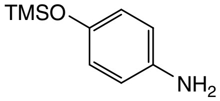
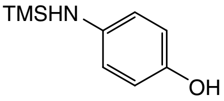
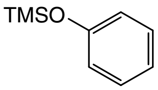
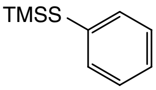
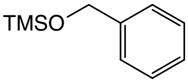
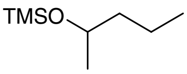
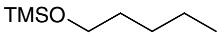
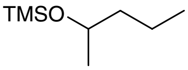
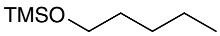
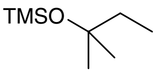
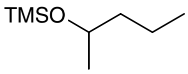
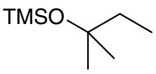
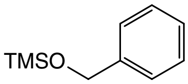
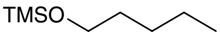
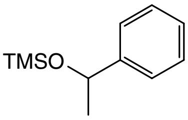
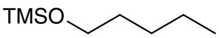
An equimolar mixture of the two competing substrates (as indicated in Table 2) was treated with deficient amounts of HMDS (0.5 equivalent) until TLC and GC experiments showed complete disappearance of one of the two starting substrates. GC analysis of the mixture quantified the relative formation of each of the two products.

Table 1. Fe_3O_4 mediated silylation of alcohols using HMDS

Entry	Substrate	Product		Yield (%)[a]
1			**1a**	98
2			**1b**	97
3			**1c**	95
4			**1d**	93
5			**1e**	97
6			**1f**	96
7	$HOCH_2(CH_2)_3CH_3$	$TMSOCH_2(CH_2)_3CH_3$	**1g**	98
8	$HOCH_2(CH_2)_2Ph$	$TMSOCH_2(CH_2)_2Ph$	**1h**	92
9	$HOH_2CC{\equiv}CH$	$TMSOH_2CC{\equiv}CH$	**1i**	88
10	$HO(H_3C)HCC{\equiv}CH$	$TMSO(H_3C)HCC{\equiv}CH$	**1j**	87
11	$HOCH(CH_3)(CH_2)_2CH_3$	$TMSOCH(CH_3)(CH_2)_2CH_3$	**1k**	85
12			**1l**	92
13			**1m**	99
14			**1n**	97

[a] Isolated yields.

Table 2. Competitive TMS protection of alcohols in the presence of Fe_3O_4

Entry	Product 1	Product 2	1 : 2
1			>99 : 1
2			>99 : 1
3			>99 : 1
4			>99 : 1
5			>83 : 17
6			>99 : 1
7			>99 : 1
8			>99 : 1
9			>85 : 15

Selected spectral data

1a: colorless liquid, ^{1}H-NMR ($CDCl_3$): δ 7.34–7.23 (5H, m), 4.70 (2H, s), 0.16 (9H, s); IR (KBr): ν 1253, 1068, 643 cm^{-1}; MS (70 eV): *m/z*, 180 (M^+, 60%), 166 ($[M - CH_2]^+$, 100%), 91 ($[PhCH_2]^+$, 88%), 79 ($[Me_3SiO]^+$, 26%), 77 (Ph^+, 38%), 73 ($[Me_3Si]^+$, 69%).
1c: colorless liquid, ^{1}H-NMR ($CDCl_3$): δ 7.31–7.19 (4H, m), 4.72 (2H, s), 0.10 (9H, s); IR (KBr): ν 1253, 1095, 844 cm^{-1}; MS (70 eV): *m/z*, 225 (M^+, 3%), 210 ($[M - CH_3]^+$, 60%), 180 (100%), 136 ($[O_2NC_6H_4CH_2]^+$, 44%), 79 ($[Me_3SiO]^+$, 50%), 73 ($[Me_3Si]^+$, 57%).
1h: colorless liquid, ^{1}H-NMR ($CDCl_3$): δ 7.22–7.18 (5H, m), 3.60 (2H, t, $J = 6.5$ Hz), 2.68 (2H, t, $J = 8$ Hz), 1.85 (2H, m), 0.11 (9H, s); IR (KBr): ν 1251, 1100, 841 cm^{-1}; MS (70 eV): *m/z*, 208 (M^+, 30%), 193 ($[M - CH_3]^+$, 28%), 118 (100%), 91 ($[PhCH_2]^+$, 48%).
1n: colorless liquid, ^{1}H-NMR ($CDCl_3$): δ 7.847.11 (7H, m), 0.39 (9H, s); IR (KBr): ν 1631, 1599, 1255, 854 cm^{-1}; MS (70 eV): *m/z*, 216 (M^+, 100%), 201 ($[M - CH_3]^+$, 55%), 73 ($[Me_3Si]^+$, 13%).

Results and Discussion

Table 1 summarizes the results for solvent-free TMS protection of various alcohols and phenols with HMDS in the presence of Fe_3O_4 particles. Initially, we examined the reaction of equimolar amounts of benzyl alcohol and HMDS with various amounts of Fe_3O_4. Investigations revealed that 10 mol% quantities of Fe_3O_4 are sufficient for nearly quantitative conversion of the starting alcohol to its respective protected moiety (entry 1) within a 5 min time period. Other benzylic and furfuryl alcohols behaved similarly well under the same conditions (entries 2–6) within the same time periods.

Figure 1. A reaction mixture in the absence (i) or presence of a magnetic field (ii).

Aliphatic alcohols were next subjected to the same conditions. As a result, the corresponding TMS ethers of both primary (entries 7–9) and secondary (entries 10–12) alcohols were obtained in high yields within comparable time periods. In contrast, *tert*-butanol remained intact even after several hours treatment under the same conditions. Finally, phenol and 1-naphthol (entries 13 and 14) were protected equally well using the same procedure giving 99 and 97% yields, respectively. In all reactions, the catalyst was simply recovered from the reaction mixture by applying an external permanent magnet (Fig. 1) and products were isolated in good purity by removing the volatile portion under reduced pressure. Further, the recovered Fe_3O_4 was successfully reused in next 10 reactions without significant loss of the catalytic performance.

The importance of the selectivity issue in synthetic organic chemistry persuaded us to design competitive reactions in order to evaluate the chemoselectivity of the protocol. The results, summarized in Table 2, clearly illustrate exclusive protection of phenols in the presence of aromatic amine (entries 1 and 2) or thiophenol (entry 3) competitors. This is also the case for primary benzylic alcohols when they are subjected to reaction with HMDS in the presence of secondary hydroxyl groups (entry 4). Under similar conditions, a primary alcohol can still be protected preferentially in competition with a secondary alcohol (entry 5), while mixtures of primary (entry 6) or secondary (entry 7) alcohols with *tert*-amyl alcohol exhibit complete preference for the protection of the less hindered competitors. It is noteworthy that a benzylic alcohol even in its secondary form is always more reactive than a primary aliphatic alcohol (entries 8 and 9).

Conclusion

This work presents an efficient protocol for room-temperature protection of alcohols and phenols in short time periods using an inexpensive and easily accessible catalyst. After physical separation of the catalyst with an external magnet, the silyl ether products are easily obtained in good purity by evaporation

Table 3. Fe_3O_4 catalyzed TMS protection of alcohols in comparison with other methods

Conditions	Solvent requirement	Reference
Fe_3O_4	–	Present work
Phosphomolybdic acid	CH_2Cl_2	[26]
TMSCl	CH_2Cl_2	[24]
Montmorillonite K-10	CH_3OH/CH_2Cl_2	[28]
$LaCl_3$	CH_2Cl_2	[39]
zeolite	EtOAc[a]	[30]
$InBr_3$	CH_2Cl_2	[43]
NH_4SCN	CH_2Cl_2	[41]

[a] Used in work-up step.

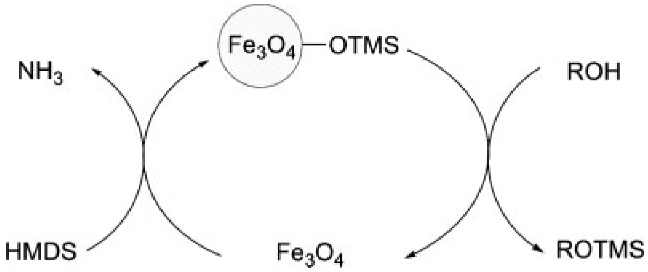


Figure 2. Possible recycling mechanism.

of the volatile portion of the reaction mixtures. We can reach at a better conclusion by comparing the performance of the present work with some other recent reports available in the literature, as illustrated in the Table 3 for TMS protection of alcohols with HMDS. Use of no other additive or co-catalyst, no solvent requirement in any of the steps, full recoverability of the catalyst upon completion of the reaction and chemoselectivity of the process are other advantages of the present work. Based on these results a mechanistic pathway, as depicted in Fig. 2, can be offered for the reactions in which the catalyst is continuously reused.

Acknowledgment

Partial financial support of this work by the Ministry of Science, Research, and Technology of Iran is greatly appreciated.

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