



Iron(III) trifluoroacetate [Fe(F₃CCO₂)₃] as an easily available, non-hygroscopic, non-corrosive, highly stable and a reusable Lewis Acid catalyst: Efficient O-silylation of α-hydroxyphosphonates, alcohols and phenols by hexamethyldisilazane (HMDS) under solvent-free conditions

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ABSTRACT

O-Silylation of hydroxyl groups of α-hydroxyphosphonates, primary, secondary tertiary-alcohols and phenols with HMDS was achieved in high to excellent yields using iron(III) trifluoroacetate [Fe(F₃CCO₂)₃] as an easily available and a cost effective, non-hygroscopic, non-corrosive, highly stable and an efficient catalyst under solvent-free conditions. As a typical reaction, we have scaled up silylation of diphenyl methanol to 20 mmol of the substrate in order to show that the catalyst is quite effective for scaled up operation. The catalyst was easily isolated by simple filtration and recycled for silylation of diphenyl methanol for several runs without losing its catalytic activity.

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1. Introduction

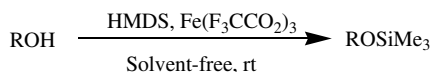
Protection of functional groups is an important sequence in multi-step syntheses of complex organic molecules. The role of silyl groups has already been recognized as an important part of organic chemistry from both analytical and synthetic point of views, especially as protecting group in many syntheses with reasonable complexity [1–3]. Trimethylsilyl group (Me₃Si) is one of the most popular and a widely used tool for masking hydroxyl functional groups. This transformation enhances solubility in non-polar solvents, increases thermal stability and in addition trimethylsilylation of hydroxyl compounds is used extensively to increase volatility of the compounds for gas chromatography and mass spectrometry as well. Several methods have been reported for this aim, including the reaction of an alcohol with trimethylsilyl halides in the presence of stoichiometric amount of a tertiary amine [4,5], with trimethylsilyl triflate, which is more reactive than the chloride [6], with R₃Si–H activated by dirhodium(II) perfluorooctanoate [Rh₂(PFO)₄] [7], with Ph₂P–SiEt₃ in the presence of diethyl azodicarboxylate

(DEAD)/pyridinium *p*-toluenesulfonate (PPTS) [8], with allylsilanes in the presence of catalytic amounts of *p*-toluenesulfonic acid [9], iodine [10], trifluoromethanesulfonic acid [11], or Sc(OTf)₃ [12], (Me₃Si)₂ catalyzed by PdCl(η³-C₃H₅)₂/PPh₃ [13]. Some of these methods suffer from use of expensive silylating agents and catalysts, using hazardous chemicals such as DEAD and also not easily available reagents or catalysts and highly moisture sensitive compounds [6–8].

Hexamethyldisilazane (HMDS) has been used as a source of Me₃Si moiety for protection of hydroxyl groups. HMDS is an inexpensive and commercially available compound. Its handling does not require special precautions, and the workup of the reaction mixture is not a time-consuming process because the by product of the reaction is ammonia. For these reasons, this compound is very popular silylating agent and its use for masking functional groups specially the–OH ones is of interest and demands. The main problem of using HMDS for the above mentioned transformation is its slow rate of the reaction. However, varieties of catalysts have been developed and introduced to promote the rate of the reaction by this silylating agent [14–25]. Along this line, we have introduced catalysts for the activation of HMDS such as; ZnCl₂ [26], N-liganded metal chlorides [27], I₂ [28], metalloporphyrins [29], tungstophosphoric acid [30] and triflates such as; Al(OTf)₃ [31], Cu(OTf)₂ [32] and Mg(OTf)₂ [33].

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Scheme 1.

Even though, the silylation ability of HMDS has been promoted in the presence of these catalysts, yet some drawbacks such as long reaction times, drastic reaction conditions and sometimes, according to the nature of the catalyst, tedious workup is an obligatory process. However, in order to eliminate or minimize the existing problems for this important reaction, introduction of new catalysts which are cost effective, recyclable, none-corrosive, non-hygroscopic with high efficiency is of demand, especially for large-scale operations.

Iron(III) chloride (FeCl_3) has emerged as a potential catalyst in affecting various organic transformations due to its high catalytic activity, availability and economic viability [40]. However, serious technical problems encountered using FeCl_3 such as; being high hygroscopic, and also a highly corrosive material. Therefore, replacement of FeCl_3 with a non-hygroscopic and a non-corrosive salt of iron(III) is worthy of attention and is of practical importance. For this purpose, iron(III) trifluoroacetate [$\text{Fe}(\text{F}_3\text{CCO}_2)_3$] which is a cost effective, stable, efficient, and non-corrosive and a moisture resistant compound has been prepared to be used as a catalyst in organic reaction. $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ is easily prepared in a quantitative yield as a red-break powder by the addition of FeCl_3 to the refluxing trifluoroacetic acid. The handling of this salt is easy and safe and can be stored in a capped bottle in the laboratory for months without observable change in its physical and chemical properties. To the best of our knowledge, the use of this compound as a catalyst is rare in the literature. However, we have employed $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ as an effective catalyst for the efficient ring opening of epoxides with ROH, H_2O , AcOH, Cl^- , Br^- , I^- , SCN^- , NO_3^- nucleophiles [34].

Now in this communication, we report another important catalytic activity of $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ for the activation of HMDS for protection of different hydroxyl groups as their trimethyl silyl ethers at room temperature under solvent-free conditions (Scheme 1).

2. Experimental

2.1. General remarks

Chemicals were purchased from Merck and Fluka Chemical Companies. All the products are known and were characterized by comparison of their physical data with those reported in the literature. IR spectra were run on a Shimadzu model 8300 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250. The purity of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV₂₅₄ plates or by a Shimadzu Gas Chromatograph GC-14A instrument with a flame ionization detector.

2.2. General procedure for the silylation of hydroxyl group of alcohols, phenols and α -hydroxyphosphonates

To a mixture of hydroxyl compound (1.0 mmol) and HMDS (0.7–1.5 mmol, 0.113–0.226 g) was added 2.5–5 mol% of $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ at room temperature and the resulting mixture was stirred by a glass rod. The progress of the reaction was monitored by TLC or GC. After completion of the reaction, 10 mL of an organic solvent (CH_2Cl_2 , Et_2O or petroleum ether) was added to the reaction mixture and filtered. The organic layer was washed with 10 mL of water and dried over anhydrous Na_2SO_4 . Highly pure

product (GC) was isolated in high to excellent yields (90–97%) after evaporation of the solvent (Tables 2 and 3).

2.2.1. Semi large-scale silylation of diphenyl methanol as a typical procedure

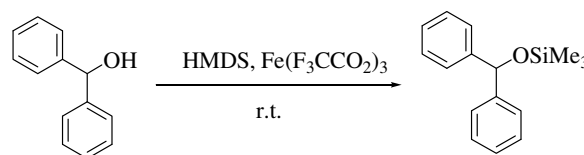
To a mixture of diphenyl methanol (20 mmol, 3.44 g) and HMDS (14 mmol, 2.26 g), $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ was added (0.5 mmol, 0.14 g) at room temperature and the resulting mixture was stirred vigorously by a mechanical stirrer. The progress of the reaction was monitored by TLC or GC. After completion of the reaction (30 min), 20 mL of an organic solvent (CH_2Cl_2 , Et_2O or petroleum ether) was added to the reaction mixture and the catalyst was filtered and separated for recycling. The organic layer was washed with water (10 mL) and dried over anhydrous Na_2SO_4 . Highly pure product (GC) was isolated in 95% yield after evaporation of the solvent (Table 2, entry 10).

3. Results and discussion

Due to the current challenges for developing solvent-free and environmentally less hazardous synthetic methods [35,36], we have studied the solvent-free reaction of diphenylmethanol as a model compound with HMDS in the presence of a catalytic amount of $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ at room temperature. The optimized molar ratio of diphenylmethanol/HMDS/ $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ was found to be 1 mmol/0.7 mmol/2.5 mol% in order to complete the reaction within 10 min producing the desired silyl ether in 95% isolated yield (Table 1, entry 1). The catalyst was easily separated and isolated by simple filtration after addition of an organic solvent such as petroleum ether, Et_2O or CH_2Cl_2 to the reaction mixture. The isolated catalyst was reused for the similar reaction for three runs without observable loss of its catalytic activity (Table 1, entries 1–3). In order to show that the catalyst is also active in solution, the reaction of diphenylmethanol (1 mmol) with HMDS (0.7 mmol) in the presence of a catalytic amount (2.5 mol%) of $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ in CH_2Cl_2 has been studied at room temperature. The reaction proceeded well and the desired silyl ether was isolated in 95% yield within 20 min (Table 1, entry 4). As it is evident from the results, the reaction rate in solution is rather slower than the similar reaction proceeded in the absence of solvent. In the absence of the catalyst similar reaction did not proceed properly in CH_2Cl_2 solution (Table 1, entry 5) even after 24 h (<8% by GC).

However, then we applied similar solvent less conditions to structurally diverse primary, secondary and tertiary alcohols and phenols. The reactions proceeded well at room temperature to yield the desired silyl ethers in excellent yields (Table 2, entries 1–15). We have learnt that for completion of silylation of substrates

Table 1
Silylation of diphenylmethanol by HMDS catalyzed by $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ at room temperature



Entry	Run	Solvent	Time (min)	Yield (%)
1	1st	–	10	95
2	2nd	–	12	93
3	3rd	–	12	94
4	1st	CH_2Cl_2	20	95
5	–	CH_2Cl_2	24 h	<8%

Table 2Results of silylation of different –OH groups by HMDS catalyzed by $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ at room temperature

Entry	Product	Time (min)	Yield (%)
1		5	92
2		5	90
3		5	95
4		30	92
5		10	91 ^a
6		12	94
7	$\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{OSiMe}_3$	10	93
8		45	90
9		15	96
10		10	95 ^b
11		2.5h	93 ^a
12		3h	90 ^a
13		20	90
14		20	95
15		20	92

^a The molar ratio of substrate/HMDS/ $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ (1/1.5/0.05) and in order to complete the reaction five drops of CH_2Cl_2 is added to the reaction mixture per 1 mmol of the substrate.

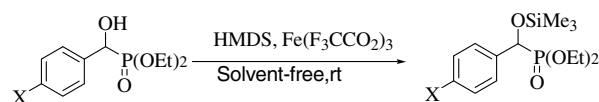
^b For easier recycling of the catalyst and also showing that the reaction is suitable for the large-scale operations, we have scaled up this reaction to 20 mmol of the alcohol without observable difficulties.

(Table 2, entries 5, 11, 12) addition of five drops of CH_2Cl_2 per 1 mmol of the alcohols was required.

α -Trimethylsilyloxyphosphonates are fascinating and important compounds from different aspects. They are attractive in

biology, industry and also they are useful precursors for the preparation of organic compounds. α -Acidic hydrogen of α -trimethylsilyloxyphosphonates can be deprotonated with bases such as lithium diisopropylamide to generate relatively stable α -carbanionic species. However, C–P and Si–O bonds present in α -trimethylsilyloxyphosphonates are easily hydrolyzed by acids or bases. Therefore, the *in situ* generated α -carbanionic species become important synthons which are equivalent to acyl anions and can take part in carbon-carbon bond forming reactions. They can react with various acylating agents to produce the α -acylated products. These can be easily converted to α -hydroxy ketones after alkaline hydrolysis of Si–O bond followed by elimination of dialkyl phosphate. β,γ -Unsaturated ketones, carboxylic acids, and unsymmetrical ketones can be prepared by alkylation of this carbocationic species [37–44]. Considering these vast applications, silylation of α -hydroxyphosphonates becomes a highly important practical transformation in organic synthesis. However, we have also considered silylation of diethyl α -hydroxyphosphonates by HMDS catalyzed by $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ at room temperature. The reactions proceeded well to completion with excellent isolated yields in short reaction times. We have found that for completion of the reaction of substrate (Table 3, entry 4) the addition of a few drops of CH_2Cl_2 to the reaction mixture facilitated the reaction to proceed to completion in a short reaction time.

C–P and Si–O bonds are sensitive towards reaction conditions and usually undergo cleavage. The almost isolated quantitative yields (Table 3) of the reactions indicate that C–P and Si–O bonds tolerate these mild reaction conditions, which are an advantage of this method. In order to show this advantage, we have compared

Table 3Results of silylation of –OH groups of α -hydroxyphosphonates by HMDS catalyzed by $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ at room temperature^a

Entry	Product	Time (min)	Isolated yield (%) ^a
1		10	97
2		10	95
3		10	96
4		20	95 ^b
5		10	95

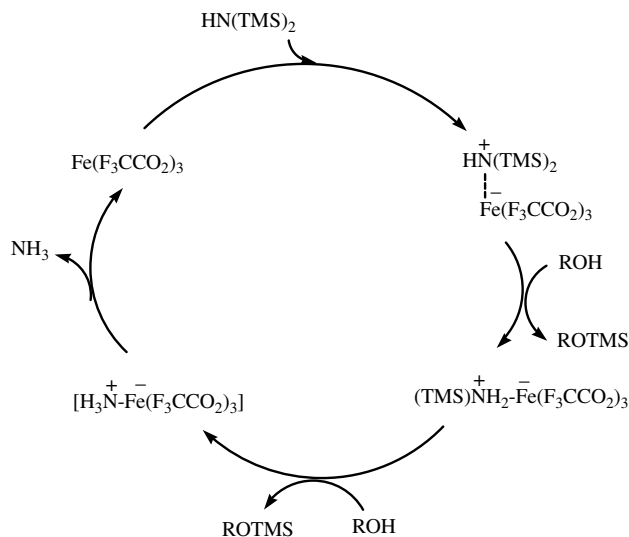
^a Conversion of the substrates to the corresponding silyl ethers was quantitative based on ¹H NMR and the molar ratio of substrate/HMDS/ $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ is 1/1.5/0.05.

^b In order to complete this reaction five drops of CH_2Cl_2 per 1 mmol of the substrate is added to the reaction mixture.

Table 4

Comparison of silylation of α -hydroxy (phenylmethyl)phosphonite by HMDS catalyzed by $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ and some other Lewis acids [31] at room temperature

Entry	Lewis Acid	Time (min)	%Conversion based on ^1H NMR
1	$\text{Fe}(\text{F}_3\text{CCO}_2)_3$	10	100
2	$\text{Al}(\text{OTf})_3$	Immediate	100
3	$\text{Cu}(\text{OTf})_2$	270	60
4	$\text{Ce}(\text{OTf})_4$	180	80
5	$\text{Hg}(\text{OTf})_2$	600	10
6	FeCl_3	90	80
7	AlCl_3	270	80
8	MgCl_2	390	50



silylation of diethyl α -hydroxy (phenylmethyl)phosphonate (Table 3, entry 2) by HMDS catalyzed by $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ with some other Lewis acids used for this conversion (Table 4). As it is evident from the results presented in Table 4, both $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ and $\text{Al}(\text{OTf})_3$ show more or less similar effective activities although the other Lewis acids were sluggish and not suitable for this conversion.

Evolution of NH_3 gas in all these reactions was observed. In addition, $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ was easily isolated and recycled without losing its catalytic activity. By considering these observations, we have qualitatively proposed a mechanism that is shown in Scheme 2.

4. Conclusions

In this study, we have introduced $\text{Fe}(\text{F}_3\text{CCO}_2)_3$ as an easily prepared, cost effective, eco-friendly, non-hygroscopic, non-corrosive, stable and easy handling catalyst for efficient trimethyl silylation of alcohols and phenols by HMDS. In addition, in the presence of this catalyst, diethyl α -trimethylsilyloxyphosphonates which are attractive compounds in biology, industry and also they are potential precursors for the preparation of useful organic compounds, were prepared in excellent yields without cleavage of C–P bonds. Except in rather few cases all reactions proceeded under solvent-

free conditions at room temperature in excellent yields. The other strong feature of the method is the simple isolation of the catalyst and its recycling for several runs without losing its catalytic activity.

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References

- [1] P.G.M. Wuts, T.W. Greene, *Green's Protective Groups in Organic Synthesis*, 4th ed., John Wiley & Sons, Hoboken, NJ, 2007.
- [2] M. Lalonde, T.H. Chan, *Synthesis* (1985) 817.
- [3] M.A. Brook, *Silicon in Organic, Organometallic, and Polymer Chemistry*, Wiley, New York, 2000.
- [4] T. Morita, Y. Okamoto, H. Sakurai, *Tetrahedron Lett.* 21 (1980) 835.
- [5] T. Vesoglu, L.A. Mitscher, *Tetrahedron Lett.* 22 (1981) 1299.
- [6] A. Bifiss, E. Castello, M. Zecca, M. Basato, *Tetrahedron* 57 (2001) 10391.
- [7] M. Hayashi, Y. Matsuura, Y. Watanabe, *Tetrahedron Lett.* 45 (2004) 1409.
- [8] A. Hosomi, H. Sakurai, *Chem. Lett.* 85 (1981) 880.
- [9] T. Veysoglu, L.A. Mitscher, *Tetrahedron Lett.* 22 (1981) 1299.
- [10] A. Hosomi, H. Sakurai, *Chem. Lett.* (1981) 85.
- [11] G.A. Olah, A. Husain, B.G.B. Gupta, G.F. Salem, S.C. Narang, *J. Org. Chem.* 46 (1981) 5212.
- [12] T. Suzuki, T. Watahiki, T. Oriyama, *Tetrahedron Lett.* 41 (2000) 8903.
- [13] E. Shirakawa, K. Hironaka, H. Otsuka, T. Hayashi, *Chem. Commun.* (2006) 3927.
- [14] B. Karimi, B. Golshani, *J. Org. Chem.* 65 (2000) 7228.
- [15] S.H. Langer, S. Connell, J. Wender, *J. Org. Chem.* 23 (1958) 50.
- [16] P. Gauuret, S. El-Ghamarli, A. Legrand, D. Couirier, B. Rigo, *Synth. Commun.* 26 (1996) 707.
- [17] Z.H. Zhang, T.S. Li, F. Yang, C.G. Fu, *Synth. Commun.* 28 (1998) 3105.
- [18] M.M. Mojtahedi, M.R. Saidi, M. Bolourtchian, M. Heravi, *Phosphorus, Sulfur Silicon Relat. Elem* 177 (2002) 289.
- [19] V.H. Tillu, V.H. Jadhav, H.B. Borate, R.D. Wakharkar, *Arkivok* (2004) 83.
- [20] N. Azizi, M.R. Saidi, *Organometallics* 23 (2004) 1457.
- [21] N. Azizi, R. Yousefi, M.R. Saidi, *J. Organomet. Chem.* 691 (2006) 817.
- [22] A. Khazaei, M.A. Zolfigol, Z. Tanbakouchian, M. Shiri, K. Niknam, J. Saïen, *Catal. Commun.* 8 (2007) 917.
- [23] R. Ghorbani-Vaghei, M.A. Zolfigol, M. Chegeny, H. Veisi, *Tetrahedron Lett.* 47 (2006) 4505.
- [24] A.V. Narsaiah, *J. Organomet. Chem.* 692 (2007) 3614.
- [25] D. Zareyee, B. Karimi, *Tetrahedron Lett.* 48 (2007) 1277.
- [26] H. Firouzabadi, B. Karimi, *Synth. Commun.* 23 (1993) 1633.
- [27] H. Firouzabadi, A.R. Sardarian, Z. Khayat, B. Karimi, S. Tangestaninezhad, *Synth. Commun.* 27 (1997) 2709.
- [28] H. Firouzabadi, N. Iranpoor, S. Sobhani, *Tetrahedron Lett.* 43 (2002) 3653.
- [29] H. Firouzabadi, A.R. Sardarian, Z. Khayat, *Iran. J. Chem. Chem. Eng.* 15 (1996) 91.
- [30] H. Firouzabadi, N. Iranpoor, K. Amani, F. Nowrouzi, *J. Chem. Soc., Perkin Trans. 1* (2002) 2601.
- [31] H. Firouzabadi, N. Iranpoor, S. Sobhani, S. Ghassamipour, *Synthesis* (2005) 595. and the references cited therein.
- [32] H. Firouzabadi, N. Iranpoor, S. Sobhani, S. Ghassamipour, Z. Amoozgar, *Tetrahedron Lett.* 44 (2003) 891. and the references cited therein.
- [33] H. Firouzabadi, N. Iranpoor, S. Sobhani, S. Ghassamipour, *J. Organomet. Chem.* 689 (2004) 3197. and the references cited therein.
- [34] N. Iranpoor, H. Adibi, *Bull. Chem. Soc. Jpn.* 73 (2000) 675.
- [35] K. Tanaka, F. Toda, *Chem. Rev.* 100 (2000) 1025.
- [36] R.S. Varma, *Green Chem.* (1999) 43.
- [37] M.M. Kabachnik, E.V. Synatkova, Z.S. Novikova, G.L. Abramova, N.G. Rozhkova, E.I. Andreeva, *Vesthn. Mosk. Univ. Ser. 2: Khim.* 31 (1990) 384.
- [38] G.H. Birum, G.A. Richardson, US Patent, 3,113,139 (to Monsanto Chem. Co), December, 3 (1963); *Chem. Abstr.* 60 (1964) 5551d.
- [39] R.E. Koenigkramer, H. Zimmer, *Tetrahedron Lett.* 21 (1980) 1017.
- [40] G.A. Olah, A. Wu, *J. Org. Chem.* 56 (1991) 902.
- [41] M. Sekine, M. Nakajima, T. Hata, *Bull. Chem. Soc. Jpn.* 54 (1982) 218.
- [42] T. Hata, A. Hashizume, M. Nakajima, M. Sekine, *Tetrahedron Lett.* 19 (1978) 63.
- [43] M. Sekine, M. Nakajima, A. Kume, A. Hashizume, *Bull. Chem. Soc. Jpn.* 55 (1982) 224.
- [44] K. Trusedale, J.M. Takacs, *Tetrahedron Lett.* 29 (1978) 2495.