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Polymethylhydrosiloxane (PMHS)/trifluoroacetic acid (TFA): a novel system for reductive amination reactions

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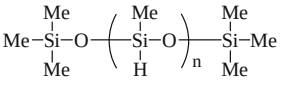
ABSTRACT

Polymethylhydrosiloxane (PMHS)/trifluoroacetic acid (TFA) was discovered as a novel metal-free system for reductive amination reactions. A variety of (het)aryl amines as well as a representative carbamate and urea were successfully alkylated by benzaldehyde in the presence of PMHS and TFA in dichloromethane at room temperature in moderate to excellent yields (28–87%). Furthermore, this reaction protocol was successfully applied to the alkylation of *p*-nitroaniline with a wide range of aldehydes, ketones, and a representative acetal to obtain the alkylated products in yields ranging from 40% to 92%. The current work represents one of the very few examples of PMHS being activated by a Brønsted acid.

Polymethylhydrosiloxane (PMHS) has been reported as an air and moisture stable, inexpensive, non-toxic, versatile, and widely used reducing agent in organic synthesis.[1]

PMHS: 

This reagent has minimal or no reducing ability in the absence of an activator, usually a transition metal catalyst or fluoride. Examples of such activators include Pd(0, II),[2] Ti(IV),[3] Zn(II),[4] Ru(0),[5] Cu(I, II),[6] In(III)[7a] and Cd(II),[7a] Ir(I, III),[7b] Tin(IV),[8] fluoride,[9] $B(C_6F_5)_3$,[10] and I_2.[11] Once activated, PMHS becomes a powerful reagent that can effectively perform a wide range of reactions, such as dehalogenation of halogenated arenes,[2e,f] reduction of ketones[3a,4a–c,6c] and esters[3d], reduction of imines,[3b,4c,d,7a,b,8] carboxamides,[5] nitro compounds,[2d] and amine N-oxides[2b], conversion of acid chlorides to aldehydes,[2c] conjugate reductions,[6a,b,10b] and hydroiodination of alkenes and alkynes.[11a] In addition, PMHS together with CsF has been reported to facilitate the Sonogashira reaction[9c] and cross-coupling of alkynes or benzothiazoles with various halides.[9b]

In efforts focused on the reductive amination of poorly reactive, electron-deficient anilines, we found that conventional reductive amination reaction conditions[12] gave either meager yields or were completely ineffective. Pursuit of a more efficient method led to the discovery of the PMHS/TFA combination which offered a novel, simple, efficient, inexpensive, and safe system for direct reductive amination reactions. The reaction system was also found to be successful with a primary carbamate and a urea as the amine source, as well as an acetal as the alkylating agent. This work represents one of the very few examples of PMHS being activated by a Brønsted acid.

Stirring a solution of benzaldehyde (106 mg, 1.0 mmol), aniline (112 mg, 1.2 mmol), and PMHS (120 mg, 2.0 mmol of –MeSi(H)O– unit) in dichloromethane overnight at room temperature did not afford any desired product. However, upon addition of the Brønsted acid TFA to the reaction mixture, the desired reductive amination product was observed. Screening an array of solvents (dichloromethane, toluene, THF, etc.), PMHS reagent quantities (1–5 equiv), and reaction concentrations (0.1–5 M) led to the identification of more optimal reaction conditions. Thus, in a typical operation,[13] a carbonyl compound and an amine were stirred in a mixture of TFA and dichloromethane [1:2 (v/v) ratio] at room temperature for circa 12 h to form an imine intermediate, which was reduced in situ by the addition of PMHS with continuous stirring for another 8–10 h at the same temperature at which point, the reaction was usually complete as indicated by TLC analysis. The results for reductive amination of benzaldehyde with various amines, a primary carbamate, and a primary urea under these optimized conditions are shown in Table 1.

It was found that anilines bearing a variety of functionalities were alkylated smoothly in good yields (entries 1–4) with functional groups, such as NO_2, CN, and methylsulfonyl, remaining unaffected. Reaction of a heteroaromatic 4-aminopyridine gave only a modest yield (entry 7). It is interesting to note that a primary carbamate and a urea underwent successful alkylation with benzaldehyde (entries 5 and 6), however, phenylhydrazine and phenoxyamine gave only trace amounts of the desired products (entries 8 and 9). There was no reaction with an alkyl amine (entry

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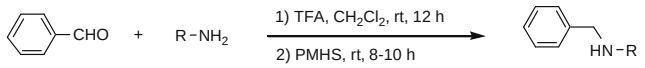
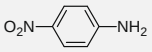
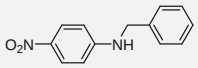
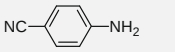
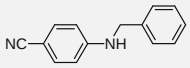
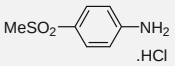
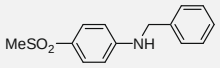
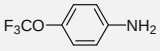
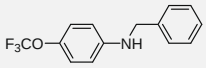
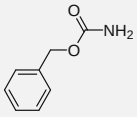
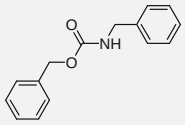
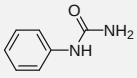
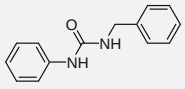
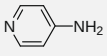
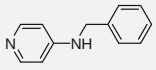
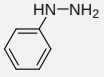
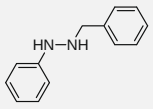
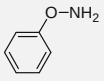
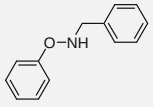
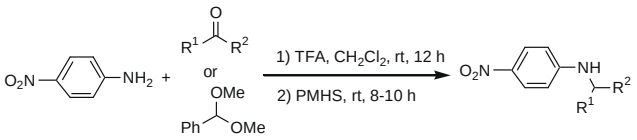
Table 1
Reductive amination of benzaldehyde with various amines as well as with a representative carbamate and urea[a]

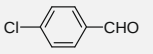
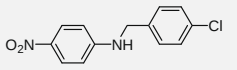
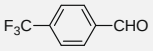
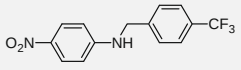
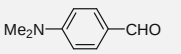
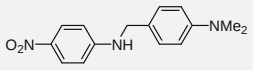
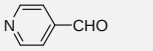
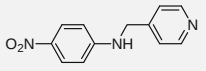
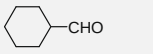
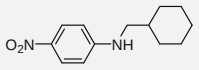
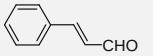
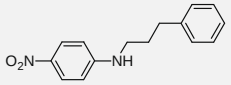
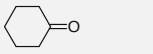
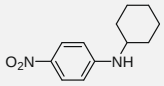
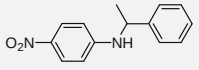
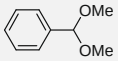
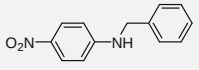


Entry	Amine	Product	Isolated yield[c] (%)
1			87
2			67
3			65
4			65
5			75
6			66
7			28[b]
8			Trace
9			Trace
10		—	0

[a] Reaction conditions: benzaldehyde (1.0 mmol), amine (1.2 mmol), PMHS (2.0 mmol of –MeSi(H)O– unit) in TFA (1 mL) and CH_2Cl_2 (2 mL), rt.
[b] Purity: 90%.
[c] Average yields of at least two runs of the same reaction.

Table 2
Reductive amination of *p*-nitroaniline with various carbonyl compounds and a representative acetal[a]



Entry	Carbonyl compound or acetal	Product	Isolated yield[b] (%)
1			73
2			77
3			57
4			75
5			55
6			40
7			50
8			40
9			92

[a] Reaction conditions: carbonyl compound or acetal (1.0 mmol), *p*-nitroaniline (1.2 mmol), PMHS (2.0 mmol of –MeSi(H)O– unit) in TFA (1 mL) and CH_2Cl_2 (2 mL), rt.
[b] Average yields of at least two runs of the same reaction.

10). One possible explanation is that the nucleophilicity of this highly basic aliphatic amine is greatly reduced in the TFA-containing reaction solution, which prevents the amine from reacting with the carbonyl reactant. It was also noted that the HCl salt of an aniline can be used directly in this reaction without desalting (entry 3).

Results from the reactions of *p*-nitroaniline with a variety of carbonyl compounds and an acetal are shown in Table 2. Aromatic aldehydes with electron-withdrawing and electron-donating groups (entries 1–3), a heteroaromatic aldehyde (entry 4), and aliphatic aldehyde (entry 5) all reacted smoothly to generate the desired products in good yields. The reaction with cinnamic aldehyde, an α,β-unsaturated aldehyde, was also successful except that the carbon–carbon double bond was reduced (entry 6), a result consistent with a report by Pearlman and co-workers,[14] who observed a carbon–carbon double bond reduction of a steroid derivative using the related PMHS/hexamethyldisiloxane/pTSA system. Ketones were proven to be useful substrates in this reaction (entries 7 and 8) as was benzaldehyde dimethyl acetal which alkylated *p*-nitroaniline in 92% yield (entry 9).

Direct reductive aminations of carbonyl compounds with PMHS activated by $Ti(OPr\text{-}i)_4$[3c,e] or an Ir (I, III) catalyst[7b] have been proposed to proceed through active metal-hydride intermediates.[1a] In our metal-free PMHS/TFA system, we hypothesize that TFA plays a dual role in facilitating intermediate imine formation and activating PMHS through hypervalent silicon intermediates for the reduction of in situ formed imine.[15,16]

In conclusion, we have developed an effective, inexpensive, and versatile one-pot reductive amination method using a novel PMHS/TFA system. A variety of aromatic and heteroaromatic amines as well as a primary carbamate and a urea were successfully alkylated with a wide range of aromatic, heteroaromatic, aliphatic, α,β-unsaturated aldehydes, and an aliphatic ketone, acetophenone, and an acetal. The reaction conditions are mild enough to tolerate functionalities, such as nitro, cyano, sulfonyl, and chloro. The current reaction represents one of the very few examples of PMHS being activated by a Brønsted acid.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.048.

References and notes

1. Recent reviews: (a) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381; (b) Senapati, K. K. *Synlett* **2005**, 1960; (c) Carpentier, J.-F.; Bette, V. *Curr. Org. Chem.* **2002**, *6*, 913.
2. (a) Reddy, C. R.; Vijeender, K.; Bhusan, P. B.; Madhavi, P. P.; Chandrasekhar, S. *Tetrahedron Lett.* **2007**, *48*, 2765; (b) Chandrasekhar, S.; Reddy, C. R.; Rao, R. J.; Rao, J. M. *Synlett* **2002**, 349; (c) Lee, K.; Maleczka, R. E., Jr. *Org. Lett.* **2006**, *8*, 1887; (d) Rahaim, R. J., Jr.; Maleczka, R. E., Jr. *Org. Lett.* **2005**, *7*, 5087; (e) Rahaim, R. J., Jr.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **2002**, *43*, 8823; (f) Maleczka, R. E., Jr.; Rahaim, R. J., Jr.; Teixeira, R. R. *Tetrahedron Lett.* **2002**, *43*, 7087.
3. (a) Verdaguer, X.; Berk, S. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 12641; (b) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713; (c) Menche, D.; Arikan, F.; Li, J.; Rudolph, S. *Org. Lett.* **2007**, *9*, 267; (d) Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1995**, *60*, 7884; (e) Chandrasekhar, S.; Reddy, C. R.; Ahmed, M. *Synlett* **2000**, 1655.
4. (a) Mimoun, H.; de Laumer, J. Y.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158; (b) Bette, V.; Mortreux, A.; Savoia, D.; Carpentier, J.-F. *Tetrahedron* **2004**, *60*, 2837; (c) Bette, V.; Mortreux, A.; Lehmann, C. W.; Carpentier, J.-F. *Chem. Commun.* **2003**, 332; (d) Chandrasekhar, S.; Reddy, M. V.; Chandraiah, L. *Synth. Commun.* **1999**, *29*, 3981.
5. Motoyama, Y.; Mitsui, K.; Ishida, T.; Nagashima, H. *J. Am. Chem. Soc.* **2005**, *127*, 13150.
6. (a) Kim, D.; Park, B.-M.; Yun, J. *Chem. Commun.* **2005**, 1755; (b) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352; (c) Lipshutz, B. H.; Noson, K.; Chrisman, W. *J. Am. Chem. Soc.* **2001**, *123*, 12917.
7. (a) Ireland, T.; Fontanet, F.; Tchao, G.-G. *Tetrahedron Lett.* **2004**, *45*, 4383; (b) Mizuta, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 2195.
8. Lopez, R. M.; Fu, G. C. *Tetrahedron* **1997**, *53*, 16349.
9. (a) Nadkarni, D.; Hallissey, J.; Mojica, C. *J. Org. Chem.* **2003**, *68*, 594; (b) Gallagher, W. P.; Maleczka, R. E., Jr. *J. Org. Chem.* **2003**, *68*, 6775; (c) Gallagher, W. P.; Maleczka, R. E., Jr. *Synlett* **2003**, 537; (d) Drew, M. D.; Lawrence, N. J.; Fontaine, D.; Sehkri, L.; Bowles, S. A.; Watson, W. *Synlett* **1997**, 989.
10. (a) Chandrasekhar, S.; Reddy, C. R.; Babu, B. N. *J. Org. Chem.* **2002**, *67*, 9080; (b) Chandrasekhar, S.; Chandrashekar, G.; Reddy, M. S.; Srihari, P. *Org. Biomol. Chem.* **2006**, *4*, 1650; (c) Chandrasekhar, S.; Chandrashekar, G.; Vijeender, K.; Reddy, M. S. *Tetrahedron Lett.* **2006**, *47*, 3475; (d) Chandrasekhar, S.; Chandrashekar, G.; Babu, B. N.; Vijeender, K.; Reddy, K. V. *Tetrahedron Lett.* **2004**, *45*, 5497.
11. (a) Das, B.; Srinivas, Y.; Holla, H.; Narender, R. *Chem. Lett.* **2007**, *36*, 800; (b) Yadav, J. S.; Reddy, B. V. S.; Premalatha, K.; Swamy, T. *Tetrahedron Lett.* **2005**, *46*, 2687.
12. Recent reviews: (a) Tripathi, R. P.; Verma, S. S.; Pandey, J.; Tiwari, V. K. *Curr. Org. Chem.* **2008**, *12*, 1093; (b) Abdel-Magid, A. F.; Mehrman, S. J. *Org. Proc. Res. Dev.* **2006**, *10*, 971; (c) Baxter, E. W.; Reitz, A. B. *Org. React.* **2002**, *59*, 1.
13. *General procedure*: To a stirred solution of carbonyl compound (1.0 mmol) and amine (1.2 mmol) in dichloromethane (2 mL) was added TFA (1 mL). The mixture was stirred at room temperature for 12 h. PMHS [2.0 mmol of –MeSi(H)O– unit, Aldrich (cat#: 176206), average M_n: 1700–3200] was then added and the resulting mixture was again stirred for 8–10 h at rt. Upon completion (by TLC or LC–MS), the reaction mixture was basified with 1 M aq sodium hydroxide to pH $\approx$ 8 and extracted with dichloromethane (30 mL $\times$ 3). The combined organic phases were evaporated to dryness and the residue was purified by preparative TLC or column chromatography to give the desired product.
14. Lim, C.; Evenson, G. N.; Perrault, W. R.; Pearlman, B. A. *Tetrahedron Lett.* **2006**, *47*, 6417.
15. In order to understand the role of TFA, the reaction of preformed imine *N*-(phenylmethylidene)aniline and PMHS was carried out in dichloromethane. No reaction was observed after the reaction mixture was stirred at rt for 12 h (by LC–MS). TFA was then added and the reaction mixture was further stirred at rt for 10 h. LC–MS showed that the reaction was complete. After work up, the desired product *N*-benzylaniline was isolated in 82% yield.
16. Trifluoroacetate hypervalent silicon species are known in the literature: (a) Pestunovich, V. A.; Albanov, A. I.; Larin, M. F.; Ignat'eva, L. P.; Voronkov, M. G. *Izv. Akadem. Nauk SSSR, Ser. Khim.* **1978**, 2185; (b) Brownstein, S. *Can. J. Chem.* **1980**, *58*, 1407.