

A Single Step Reductive Amination of Carbonyl Compounds with Polymethylhydrosiloxane-Ti(OⁱPr)₄[#]

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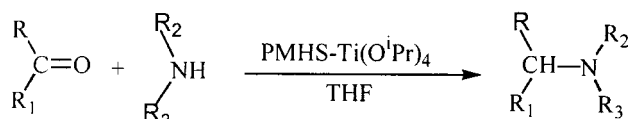
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Abstract: Highly chemoselective 'one pot' amination of carbonyl groups is achieved using polymethylhydrosiloxane (PMHS) as reductant and Ti(OⁱPr)₄ as activator. A comparative study with other activators such as AlCl₃ and Pd-C was also studied.

Key words: carbonyl compounds, amines, PMHS, reductive amination, titanium(IV)isopropoxide

The search for safe and practically useful reducing reagents is of great importance. The already existing reducing reagents such as LiAlH₄, NaBH₄, DIBAL-H, although efficient in producing high yields of desired products, are pyrophoric. Polymethylhydrosiloxane (PMHS) is being pursued as a safe and environmentally friendly reagent for the reduction of organic functional groups¹. This reagent is very inert on its own, making it safe to handle, but in the presence of a proper activator it proves itself as an excellent substitute for hydride reagents.



R, R₂ = H, alkyl or aryl



R₁, R₃ = alkyl or aryl

Equation 1

Recently, we have been engaged in the development of new methods for preparing amines² as well as exploring the utility of PMHS as a versatile reductant³ and in this context we desired an expeditious method for direct conversion of carbonyl compounds to amines via reductive amination. Here we disclose our latest findings wherein Ti(OⁱPr)₄ has been identified, as not only an efficient catalyst for imination of carbonyl compounds, but also as an effective activator of PMHS for reductive amination (Equation 1). Reductive amination is traditionally carried out by using sodium triacetoxyborohydride,⁴ zinc borohydride,⁵ dibutyltin chloride,⁶ sodium cyanoborohydride,⁷ zinc modified cyanoborohydride,⁸ or zinc-acetic acid⁹ among others,¹⁰ but all suffer from disadvantages.¹¹

Initially, benzaldehyde and benzylamine were stirred together in the presence of PMHS and potential activators (Pd-C, AlCl₃ or ZnCl₂), but to our disappointment the formation of N, N-dibenzylamine was observed only to an extent of 50% (Table 1) with no improvement on overall yield being observed with other substrates. A more careful study resulted in identification of Ti(OⁱPr)₄ as an efficient activator for PMHS as well as imine formation. Thus, benzaldehyde, benzylamine and Ti(OⁱPr)₄ were stirred for one hour, then PMHS was added and stirred at ambient temperature resulting in the clean formation of N, N-dibenzylamine in 90% yield. Several other carbonyl compounds were treated with readily available amines (both primary and secondary) and excellent yields of alkylated amines were obtained (Table 2).¹²

Table 1 Reductive Amination with PMHS Using Different Activators

carbonyl compound	amine	AlCl ₃ in Toluene time(h) / yield(%)	Pd/C in Ethanol time(h) / yield(%)	Ti(O ⁱ Pr) ₄ in THF time(h) / yield(%)
Ph-CHO	H ₂ N-Ph	12 / 40	10 / 60	5 / 90
Ph-CHO	H ₂ N-Ph	12 / 52	10 / 62	5 / 92
Ph-CH=CH-CHO	H ₂ N-Ph	10 / 48	8 / 55 ^a	4 / 85
Ph-CH=CH-CHO	H ₂ N-Ph	12 / 45	9 / 56 ^a	4.5 / 88
	H ₂ N-Ph	13 / 45	10 / 55	6 / 90
	H ₂ N-Ph	13 / 50	10 / 58	6 / 90

^a double bond reduced product

Table 2 Reductive Amination with PMHS-Ti(OⁱPr)₄

entry	carbonyl compound	amine	time(h)	product	yield(%) ^b
1			5		90
2	1		5		92
3	1		5.5		85
4			4		85
5	2		4.5		88
6	2		4.5		85
7			6		90
8	3		6		90
9	3		6		88
10			6		83
11	4		6		85
12	4		6		80
13			4.5		88
14	5		4.5		87
15	5		5		85
16			5.5		88
17			4		85

^b all yields refer to pure isolated products, characterised by ¹H NMR, mass and IR

Examples studied include the preparation of 2° amines as well as 3° amines. Entries 4, 5 and 6 clearly demonstrate that the olefinic functionality is stable to the present experimental conditions. Aliphatic keto substrates (entries 13, 14, 15 and 16) also underwent smooth reductive amination to yield desired products in excellent yields. Entry 17 demonstrates the stability of nitro group towards the present protocol.

The results presented herein indicate that PMHS-Ti(OⁱPr)₄ is a synthetically very efficient reagent combination for reductive amination of both aldehydes and ketones. The mildness of the experimental procedure, availability of reagents, safety and selectivity makes the present procedure a versatile one. In addition we have clearly demonstrated that Ti(OⁱPr)₄ is a better activator compared to AlCl₃ and Pd-C.

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References and Notes

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- (11) (a) Sodium cyanoborohydride may require up to a 5 fold excess of amine and may result in the contamination of the product with cyanide. Moreover, this reagent is highly toxic and generates byproducts HCN and NaCN, upon workup. (b) Sodium triacetoxyborohydride has limitations with aromatic and unsaturated ketones. (c) Catalytic hydrogenation is not compatible with compounds containing a double or triple bond and several other reducible functional groups such as nitro or cyano. (d) Zinc borohydride is not commercially available and is again made from sodium borohydride, which is more expensive than PMHS.
- (12) **General Experimental Procedure:** A mixture of carbonyl compound (1 mmol), amine (1 mmol) and titanium(IV)isopropoxide (0.355mg, 1.25 mmol) was stirred at room temperature. After 1 hour, PMHS (120mg, 2 mmol) dissolved in THF(5 mL) was added and the solution was stirred (Table 2). The reaction mixture was cooled and sodium hydroxide solution (3 N, 10 mL) was carefully added dropwise (at first there is vigorous gas evolution). After stirring for 20 minutes, the solution was extracted with ether (3x20 ml). The combined ether layers were washed with brine, dried (Na₂SO₄) and evaporated in vacuo to give the amine in essentially pure form.

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