

SHORT COMMUNICATION

POLYMETHYLHYDROSILOXANE REDUCTION OF CARBONYL FUNCTION CATALYSED BY TITANIUM TETRACHLORIDE

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(Received October 11, 2017; Revised January 22, 2018; Accepted January 23, 2018)

ABSTRACT. Reduction of aromatic aldehydes and ketones into the corresponding methylene derivatives by polymethylhydrosiloxane in the presence of titanium tetrachloride as catalyst was achieved in good to excellent yields ranging from 55-90%. The reaction took place under relatively mild conditions and smoothly led to the desired target molecules in the presence of other functional groups such as halogens, hydroxyl, nitro and methoxy groups. However, in the reduction of the substrate with two methoxy groups in close proximity (1,2-positions), the reaction necessitated a larger amount of the titanium catalyst and a longer reaction time to complete the reduction of the carbonyl function due to a likely complex formation of titanium tetrachloride with the methoxy groups.

KEY WORDS: Carbonyl reduction, Polymethylhydrosiloxane, Titanium tetrachloride, Catalyst, Hydride transfer

INTRODUCTION

The reduction of the carbonyl function of aldehydes and ketones to methylene is an important reaction that has found wide applications in organic syntheses both in research laboratories and also in the chemical industry. Various methods have been employed for this chemical transformation but the Clemmensen [1] and Wolff–Kishner [2] reduction processes have thus far exhibited the most general utility [3]. However, the drastic reaction conditions of both processes have given rise to various other methods, all in an effort to find milder reaction conditions. Some of the alternative methods include catalytic hydrogenation [4-5], reductions using Raney nickel in hydroxide media [6], reductions using PtO₂ [7], HI-phosphorus [8-9], NaBH₄-CF₃COOH [10-11], NaCNBH₃-BF₃Et₂O [12], LAH-AlCl₃ [13]. While these methods offer some advantages, they also suffer from some disadvantages. A good number of the methods are limited to aromatic systems, others require the use of pyrophoric hydride source for reduction, and some are prone to long reaction hours coupled with tedious workup and are associated with low yields. Since silanes undergo hydride transfer to relatively stable carbenium ions, they have been used to convert carbonyl function to methylene [3]. More recently, however, catalytic reduction of the carbonyl group has been carried out in the presence of polymethylhydrosiloxane (PMHS), an excellent hydride donor and cheap by-product of the silicone industry, which is easy to handle and claimed to be environmentally friendly [14].

Jaxa-Chamiec and co-workers [15] reported the conversion of carbonyl group to methylene using AlCl₃ in the presence of PMHS. The inherent environmental problems associated with the workup of AlCl₃ reaction systems, render this process unsustainable. A rapid defunctionalisation of carbonyl group to methylene has been described by Chandrasekhar and co-workers using B(C₆F₅)₃ as a nonconventional Lewis acid to activate PMHS [16]. Although the authors claimed that the method reduced aromatic as well as aliphatic carbonyl compounds in good yields, the high cost of B(C₆F₅)₃ is prohibitive. A promising alternative was the microwave induced

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FeCl₃.6H₂O-catalysed reduction of ketones and aldehydes to alkane compounds developed by Campagne and co-workers [14, 16] in which aromatic and aliphatic carbonyl compounds were reduced in good yields.

South Africa has the world's second deposits of titanium after Australia [17]. The east coast of the country, more specifically much of Pondoland is awash with titanium sands. It could be the gateway metal to a new golden age for South Africa. However, while titanium finds varied applications in industry, its use in organic syntheses remains largely unexplored especially as a reduction catalyst. Buchwald and co-workers [18] were able to reduce ketones and methyl esters using a titanocene catalyst in the presence of PMHS. Reduction of the carbonyl functional group of various substrates catalysed by titanium tetrachloride (tickle) in the presence of PMHS as a hydride source in dichloroethane (DCE) is herein described by the authors of this paper for the first time.

EXPERIMENTAL

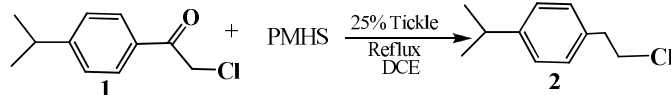
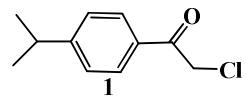
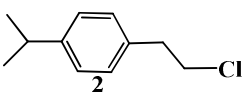
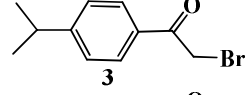
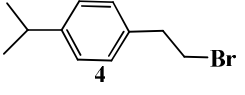
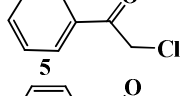
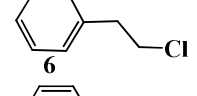
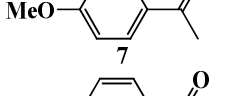
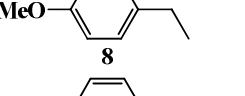
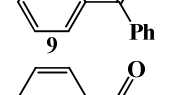
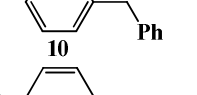
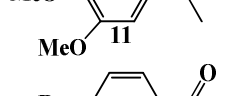
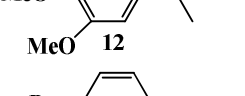
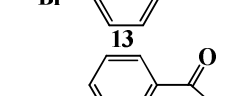
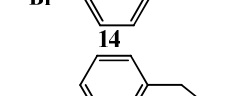
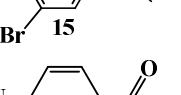
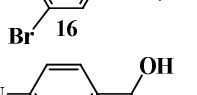
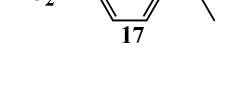
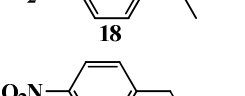
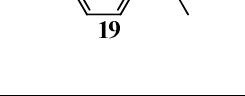
General. All chemicals were obtained from commercial sources and were used without further purification unless stated otherwise. Products were characterised by ¹H- and ¹³C-NMR spectroscopy using a Varian spectrometer at 400 and 100 MHz for proton and carbon-13, respectively. Spectra were recorded from CDCl₃ solutions employing TMS as an internal reference. All spectra are reported as δ (ppm) values.

Representative procedure (compound 2). A solution of 2-chloro-1-[4-(propan-2-yl)phenyl]ethanone (1 g, 5.1 mmol) in dichloroethane (DCE) (10 mL) was placed in a 50 mL three-mouth round-bottomed flask equipped with a reflux condenser, a calcium chloride drying tube, a thermometer and a magnetic stirring bar. To the stirred reaction solution at room temperature, tickle (0.115 mL, 25%) followed by PMHS (0.7 g, 12.2 mmol) were added from a syringe. The reaction mixture was heated to reflux and progress of the reaction monitored by thin layer chromatography (tlc) and stopped after three hours. The gelatinous reaction mixture was taken up in hexane (15 mL) and filtered under a plug of celite. The filter cake was washed with hexane (50 mL) and the filtrate concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to give an oily product (0.75 g, ~79.4%); b.p.: 140 °C/2.6 mm Hg.

¹H-NMR of **2**. δ (CDCl₃): 1.11 (d, 6H, J = 7.14), 2.77 (sept, 1H, J = 7.01), 3.01 (t, 2H, J = 7.69), 3.42 (t, 2H, J = 7.69), 7.01 (d, 2H, J = 8.24), 7.06 (d, 2H, J = 8.24). ¹³C-NMR; δ (CDCl₃): 23.96, 33.01, 33.71, 39.07, 126.63, 128.53, 136.20, 147.48; HRMS (EI⁺): calc. for C₁₁H₁₅Br, 226.0357; found 226.0361.

¹H-NMR of **4**. δ (CDCl₃): 1.16 (d, 6H, J = 7.14), 2.81 (sept, 1H, J = 7.03), 2.96 (t, 2H, J = 7.56), 3.62 (t, 2H, J = 7.41), 7.06 (d, 2H, J = 8.24), 7.11 (d, 2H, J = 8.24). ¹³C-NMR; δ (CDCl₃): 24.34, 34.08, 39.18, 45.41, 121.97, 129.07, 135.73, 147.81; HRMS (EI⁺): calc. for C₁₁H₁₅Cl, 182.0822; found 182.0777.

All products listed in Table 1 were prepared analogously to the representative procedure.

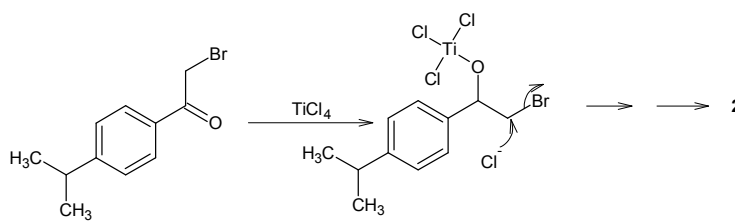
Entry	Carbonyl compound	Product	Yield (%)	Reference
				
Table 1: The PMHS Reduction of Ketones and Aldehydes Catalyzed by Tickle(25%)				
1			79.4	This work
2			89	This work
3			85	[19]
4			90	[20-21]
5			78	[20-21]
6			67	[22]
7			55	[23-24]
8			65	[25]
9			25	[26]
			50	[27]

RESULTS AND DISCUSSION

The reduction of carbonyl function by PMHS activated by tickle occurred smoothly and the formation of a gelatinous precipitate signified the end of the reaction, which was confirmed by

TLC. The reaction was complete in less than an hour with the use of 50% tickle. The tickle concentration of 25% was maintained throughout the investigations and the reactions never exceeded three hours.

Results of this reduction reaction are summarised in Table 1. Good to excellent yields were achieved using this method. Entries 1, 2, 3, 7, and 8 indicate that the presence of halogens did not interfere with the reduction reaction. It is noteworthy that reactions in entries 2 and 3 leading to the formation of compounds **4** and **6**, respectively, could be carried out at room temperature affording the same products and yields. The high reactivity of the two substrates (**3** and **5**) may be attributed to the activation of the carbonyl function by the halogen atoms. In the case of substrate **3**, two products were observed, irrespective of the reaction conditions utilised. Compound **2** most likely originated from the attack by a chlorine ion from tickle on the intermediate as outlined in Scheme 1 below:



Scheme 1

The reduction of **3** afforded a mixture of **2** and **4** in 73 and 27% yields, respectively. This was found to be true when the reaction took place at room temperature and at refluxing temperature. The identity of **2** was confirmed independently by the reaction of **4** with excess sodium chloride in DMSO to afford the product in 90% yield. An attempt to carry out this reaction in DMF resulted in substantial elimination of the halogen to form the corresponding styrene derivative. However the best method to access compound **2** was through the reduction of substrate **1** using the same methodology as shown in entry 1. To the best of our knowledge, compounds **2** and **4** have not been described before.

It is also relevant to note that there is no direct conversion of compounds **5** and **15** to the corresponding reduction products **6** and **16**, respectively. Reduction of **5** by hydrogen transfer reaction with formic acid in the presence of a ruthenium catalyst led only to the corresponding chlorohydrin (2-chloro-1-phenylethanol [28].

Even though one methoxy group did not interfere in the reduction as shown in entry 4, the two ether groups in close proximity (Entry 6) appeared to slow down the reaction but did not completely inhibit it. The reaction required 60% of tickle and took six hours to complete, due likely to the formation of a chelation complex with tickle that slowed down the reduction process.

Surprisingly however, the nitro group in substrate **17** did not inhibit the reaction despite the fact that its two oxygen atoms could potentially chelate the titanium ion. Unlike in all the other entries in table 1, the reaction led to the formation of two products: the expected methylene derivative and the corresponding alcohol. This is an indication that the reaction takes place in a two-step process with the alcohol as the intermediate. This implies that with the use of appropriate reaction conditions, it should be possible to stop the reaction at the alcohol stage or, if so desired, carried on to the final step. The formation and isolation of the alcohol intermediate may open up a new avenue for this reaction. For example, carbonyl derivatives such as imines may be selectively reduced to the corresponding amines. The Clemensen and Wolff-Kishner reductions on the other hand operate with completely different reaction mechanisms.

Although the halogens have an inductive electron-withdrawing ability, substrates **1**, **3**, **5**, **13**, and **15** revealed no noticeable influence on the outcome of the reaction.

The herein described PMHS reduction of aromatic aldehydes and ketones into the corresponding methylene derivatives catalysed by tickle compared to the classical Wolff-Kishner and Clemmensen processes has proven to be the method of choice. Its simplicity, safety of operation, low cost and functional group compatibility outweighs those of other known methods.

CONCLUSION

Carbonyl compounds were successfully reduced to the corresponding methylene derivatives using the polymethylhydrosiloxane–tickle system as the reducing agent. The mild reaction conditions, namely the ease of handling of the reagents, low reaction temperature, functional group compatibility and easy reaction workup may pave the way for possible industrial applications of this reduction reaction. The unexpected isolation of an alcohol intermediate in one example gives insight into the possible reaction steps involved in the process.

In future investigations, attempts will be made to expand the scope of this reduction reaction and perhaps determine its limitations by utilising a range of aliphatic and aromatic carbonyl compounds with a variety of functional groups.

ACKNOWLEDGMENT

We thank the Directorate of Research Development at Walter Sisulu University for financial support.

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