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An Efficient Protocol for Alcohol Protection Under Solvent- and Catalyst-Free Conditions

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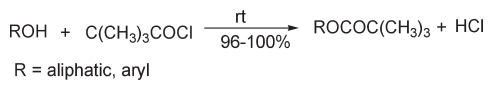


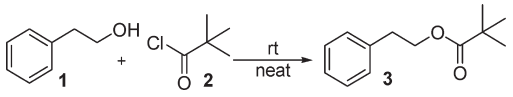
A simple and highly efficient protocol for pivaloylation of alcohols without using a catalyst under solvent-free conditions has been developed. The key advantages of the reaction are short reaction time, high yields, simple work-up, and no need for further purification. Selectivity was observed between primary alcohols vs. secondary alcohols and aliphatic alcohols vs. aromatic alcohols. The accentuated and relevant phenomenon of this method that we observed is in one-pot conversion of TBS protection into Piv protection of the hydroxyl group.

In recent years, the central objective in synthetic organic chemistry is to develop a greener and more economically competitive process for multifaceted synthesis. In the aspect of total synthesis, selection of protecting groups is more pivotal. To perform selective reactions at one reactive site, others should be temporarily blocked while doing multifaceted synthesis of a multifunctional compound. Many protective groups have been, and are being developed for this purpose;[1] among these groups, pivaloylation of alcohols is an important and useful transformation for protecting various alcohols. Pivaloylation of alcohols has received considerable attention in synthesis due to the stability of the pivaloyl group toward acidic reagents and its liability in the presence of base, thus favoring the necessary transformations that are to be made with an acidic reagent. Because of the above said reasons pivaloylation serves as a stable protection for hydroxyl groups in natural product synthesis and carbohydrate chemistry.[2] The traditional methods involve the reaction of alcohols with pivaloyl chloride in the presence of Lewis acid[3a] and base,[3b] using carboxylic acid and alcohol in the presence of mineral acids,[3c−e] which are corrosive in nature and susceptible to acid labile protecting groups. Further, modified methods have been made with alcohols and acid chlorides in the presence of Lewis acids such as zinc chloride,[4a] magnesium,[4b] alumina,[4c] and clay.[4d] We reported[3a] protection of alcohols using pivaloyl chloride in the presence of La $(NO_3)_3 \cdot 6H_2O$.

However, most of these methods still have certain limitations such as expense and the air-sensitive nature of catalysts, restrictions for large-scale applications, critical product isolation procedures, and difficulty in recovery of high-boiling solvents. These methods may lead to contamination of final products with traces of transition metals and side products. The development of a simple and efficient method under green reaction conditions for selective protection of the hydroxyl group with pivaloyl chloride has been advocated. In continuation of our earlier report, we have developed such a method for protection of alcohols using pivaloyl chloride under solvent- and catalyst-free conditions.

In recent years the green context has become an eminent issue. The reactions under catalyst- and solvent-free conditions are considerably safe, nontoxic, environmentally friendly, and inexpensive. Recently, a new method has been developed for acylation of alcohols, amines, and thiols under green reaction conditions,[5a] and *N*-phosphoramino α-aminophosphonates[5b] are successfully synthesized under catalyst- and solvent-free conditions. This inspired us to focus on protection of alcohol derivatives under catalyst- and solvent-free conditions. According to our knowledge, this is the first report of solvent-free pivaloyl protection of alcohol derivatives under catalyst-free conditions.

TABLE 1. Solvent Effect for Pivaloyl Protection[a]



entry	solvent	time(min)	yields[b](%)
1	water	120	nil
2	CH_2Cl_2	30	89
3	CH_3CN	30	72
4	ether	30	83
5	neat	5	100

[a]Reaction conditions: alcohol (1.0 mmol), Piv-Cl (1.1 mmol), catalyst free, at rt. [b]Isolated yields.

In a model reaction, the 2-phenylethanol (**1**) was reacted with pivaloyl chloride (**2**) under neat conditions at room temperature to yield phenethyl pivalate (**3**) in 100% yield

(1) (a) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons Inc: New York, 1991; p 1. (b) Katritzky, A. R.; Otto, C. M.; Charles, W. R. *Comprehensive Organic Transformations*; John Wiley & Sons Inc: New York, 1996; Vol. 5. (c) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*; Wiley Interscience: New York; 1995; Vol. 7, p 5525.

(2) (a) Kigoshi, H.; Ojika, M.; Ishigaki, T.; Suenaga, K.; Mutou, T.; Sakakura, A.; Ogawa, T.; Yamda, K. *J. Am. Chem. Soc.* **1994**, *116*, 7443. (b) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Tsukada, I.; Tsuboi, T.; Ogawa, T.; Yamda, K. *J. Am. Chem. Soc.* **1994**, *116*, 7441. (c) Matsushita, Y.; Sugamoto, K.; Kita, Y.; Matsui, T. *Tetrahedron Lett.* **1997**, *38*, 8709.

(3) (a) Prabhakar, P.; Suryakiran, N.; Venkateswarlu, Y. *Chem. Lett.* **2007**, *36*, 732. (b) Robins, M. J.; Hawrelak, S. D.; Kanai, T.; Siefer, J. M.; Mengel, R. *J. Org. Chem.* **1979**, *44*, 1317. (c) Hauser, C. R.; Hudson, B. E.; Abramovisch, B.; Shivers, J. C. *Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1955; Vol. III, p 142. (d) Haslam, E. *Tetrahedron* **1980**, *36*, 2409. (e) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons, Inc.: New York, 1991.

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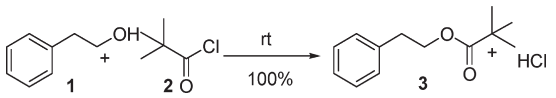
SCHEME 1

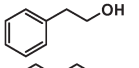
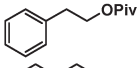
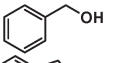
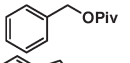
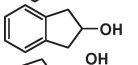
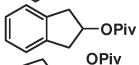
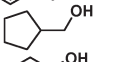
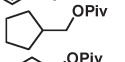
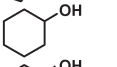
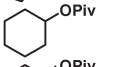
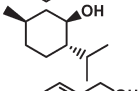
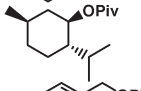
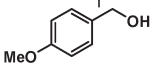
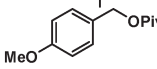
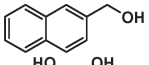
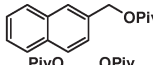
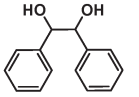
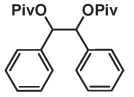
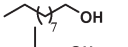
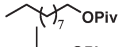
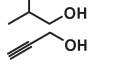
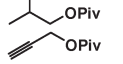
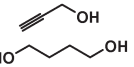
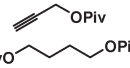
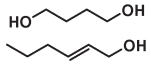
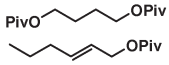
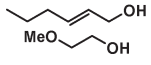
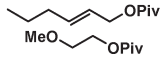
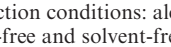
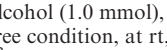


within 5 min (Table 1, entry 5) and HCl formed as a side product was removed on water workup. (Scheme 1). The final product was obtained without further purification and was characterized by ^{1}H NMR by the conspicuous presence of signal due to the *tert*-butyl group at δ 1.14 (s, 9H) along with 2-phenyl ethanoate signals.[3a]

To investigate the advantageous role of the neat conditions, we carried out the above reaction in different solvents such as water, CH_2Cl_2, MeCN, and ether under identical conditions to obtain phenethyl pivalate in 0%, 89%, 72%, and 83% yields, respectively. It is remarkable that the reaction carried out under neat conditions affords phenethyl pivalate in excellent yield (100%), which is significantly higher than that in organic solvents (Table 1, entry 5).

After screening the reaction conditions, the scope and limitations of this simple process are explored by using a wide range of structurally diverse alcohols with pivaloyl chloride. The reaction proceeds smoothly under neat conditions to afford the corresponding pivaloyl esters in excellent yields. The near completion of the reaction may be explained due to the low solubility of the gaseous HCl formed as the side product in the absence of solvent. The results are summarized in Table 2.

TABLE 2. Pivaloylation of Aliphatic Alcohols under Catalyst- and Solvent-Free Conditions[a]

entry	R-OH	R-OH	time(min)	yields[b](%)
1			5	100
2			5	100
3			15	96
4			5	100
5			15	96
6			15	92
7			5	100
8			5	100
9			15	96
10			5	100
11			5	100
12			15	100
13			15	100
14			5	100
15			5	100

[a]Reaction conditions: alcohol (1.0 mmol), Piv-Cl (1.1 mmol), under catalyst-free and solvent-free condition, at rt, The products were characterized by IR, ^{1}H and ^{13}C NMR, and mass spectroscopy. [b]Isolated yields.

TABLE 3. Pivaloylation of Aromatic Alcohols under Catalyst- and Solvent-Free Conditions[a]

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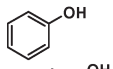
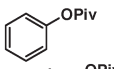
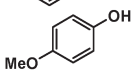
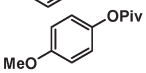
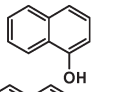
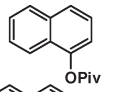
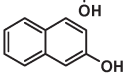
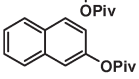
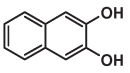
1			12	0
2			12	0
3			12	94
4			12	97
5			12	97[c]

[a]Reaction conditions: alcohol (1.0 mmol), Piv-Cl (1.1 mmol), catalyst free, at rt. [b]Yield of isolated product. [c]Piv-Cl (2.1 mmol).

The generality of the present method was also extended to phenols and naphthols as shown in Table 3. Unfortunately, all attempts to pivaloylate phenols failed. On the other hand, naphathols reacted for long periods with pivaloyl chloride resulted in the corresponding product in excellent yields.

To investigate the potential of the new method, we carried out pivaloylation of a hydroxyl group in a moiety containing sensitive groups, e.g., the TBS group (**1a**). When the reaction is carried out under neat and open vessel conditions, product **1b** is afforded exclusively under short reaction times. When performing the same reaction under closed vessel conditions for a long reaction period (12 h) in one pot, the product (**1c**) was obtained in high yield (Scheme 2,). However, if we use

SCHEME 2

excess Piv-Cl (2.1 equiv) under neat and closed vessel conditions, product **1d** is generated in longer reaction times. When both primary and secondary alcohol groups are present, e.g., **2a**, the pivaloylation occurs exclusively on the primary

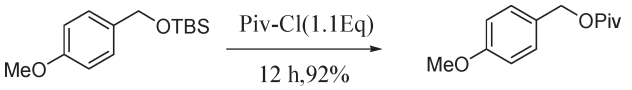
(4) (a) Baker, R. H.; Bordwell, F. G. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 141. (b) Spassow, A. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 144. (c) Pagni, R. M.; Kabalka, G. W.; Boothe, R.; Gaetano, K.; Stewart, L. J.; Conaway, R.; Dial, C.; Gray, D.; Larson, S.; Luidhart, T. *J. Org. Chem.* **1988**, *53*, 4477. (d) Laszlo, P. *Science* **1987**, *235*, 1473.

(5) (a) Ranu, B. C.; Dey, S. S.; Hajra, A. *Green Chem.* **2003**, *5*, 44–46. (b) Zhang, J.; Cui, Z.; Wang, F.; Wang, Y.; Miao, Z.; Chen, R. *Green Chem.* **2007**, *9*, 1341.

alcohols with a unimolar stoichiometry, and on both alcohols (**2b**) (Scheme 2) when >2 equiv of pivaloyl chloride is used.

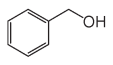
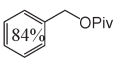
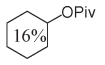
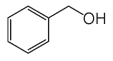
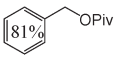
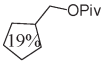
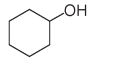
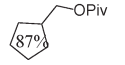
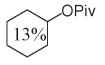
Furthermore, we have observed an important and germane phenomenon, i.e., the conversion of TBS protection into Piv protection of a hydroxyl group taking place in one pot under neat and closed vessel conditions at longer reaction times (Scheme 3).

SCHEME 3



We also investigated the chemoselectivity of the reaction. When we reacted a mixture of benzyl alcohol and cyclohexanol (1:1) with pivoloyl chloride (1 mmol), we found benzyl alcohol was protected in 84% yield and cyclohexanol in 16%. The pivaloylation of alcohols is highly chemoselective toward primary alcohol when they compete with secondary alcohols and is also highly selective toward benzyl alcohols when they compete with aliphatic alcohols (Table 4).

TABLE 4. Chemoselective Pivaloylation

s.no.	reagent 1	vs.	reagent 2	Piv-Cl, 15 Min → predominant product	minorproduct
1				 84%	 16%
2				 81%	 19%
3				 87%	 13%

[a]Reaction conditions: substrates 1:1 ratio (2.0 mmol), Piv-Cl (1 mmol), catalyst free, solvent free at rt, closed vessel condition.

In summary, we have developed a simple and efficient protocol for protection of alcohols under catalyst- and solvent-free conditions. This process eliminates the use of highly polar and volatile organic solvents and catalyst. Furthermore, the procedure offers several advantages including improved yields, simple experimental procedure, and no need for further purification. This protocol is useful in biologically active natural products synthesis and carbohydrate chemistry. The present methodology is environmentally benign.

Experimental Section

General Procedure. The pivaloylation of alcohols was carried out by simple addition of Piv-Cl (1.1 mmol) to hydroxy compound (1.0 mmol) in a 5 mL round-bottomed flask without using catalyst and solvent under closed vessel conditions. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was dissolved in 5.0 mL of DCM and washed with distilled water, then the organic layer was dried with Na_2SO_4 and solvent was evaporated under vacuum to yield the corresponding product **3** in 100% yield: colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.14 (m, 5H), 4.24 (t, 2H, $J = 6.9$ Hz), 2.91 (t, 2H, $J = 6.9$ Hz), 1.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 138.1, 129.0 (2C), 128.0 (2C), 126.5, 65.0, 38.5, 35.0, 27.0 (3C).

General Procedure for Multigram Scale. 2-Phenylethanol (about 2.44 g, 1 equiv) was reacted with Piv-Cl (about 2.5 g, 1.01 equiv) under catalyst- and solvent-free and closed vessel conditions for 30 min. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was dissolved in 80.0 mL of DCM and washed with distilled water, then the organic layer was dried with Na_2SO_4 and solvent was evaporated under vacuum to yield the corresponding product **3** (4.0 g (99%)).

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Supporting Information Available: Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.