Convenient Formation of Diphenylmethyl Esters Using Diphenylmethyl Trichloroacetimidate

Arijit A. Adhikari, Jigisha P. Shah, Kyle T. Howard, Christopher M. Russo, Daniel R. Wallach, Matthew R. Linaburg, John D. Chisholm*

Department of Chemistry, 1-014 Center for Science and Technology, Syracuse University, Syracuse, NY 13244, USA
Fax +1(315)4434070; E-mail: jdchisho@syr.edu

Received: 14.10.2013; Accepted after revision: 24.10.2013

Abstract: Diphenylmethyl trichloroacetimidate is a useful reagent for the protection of carboxylic acids as their corresponding diphenylmethyl esters. These esterifications proceed rapidly without the need for an added catalyst or promoter. A variety of carboxylic acid substrates undergo esterification in excellent yields with the trichloroacetimidate reagent, including substrates possessing acid- or base-sensitive functionality. Protection of a carboxylic acid with a highly enolizable α-stereocenter using diphenylmethyl imidate was also accomplished without racemization.

Key words: esters, protecting groups, C–O bond formation, chemoselectivity, esterification

Esters are common protecting groups for carboxylic acids and are often utilized in multistep organic synthesis. A popular choice is the diphenylmethyl (DPM) ester, as it can be removed using aqueous base, by hydrogenation, or under acidic conditions.[1] This flexibility is advantageous, as the different conditions provide options should incompatibilities with other functional groups be encountered during removal. Diphenylmethyl esters are also popular because they do not introduce new stereogenic centers or overly complicate NMR spectra. For these reasons, the diphenylmethyl protecting group has been used extensively in the synthesis of peptides,[2] β-lactam antibiotics[3] and complex natural products.[4]

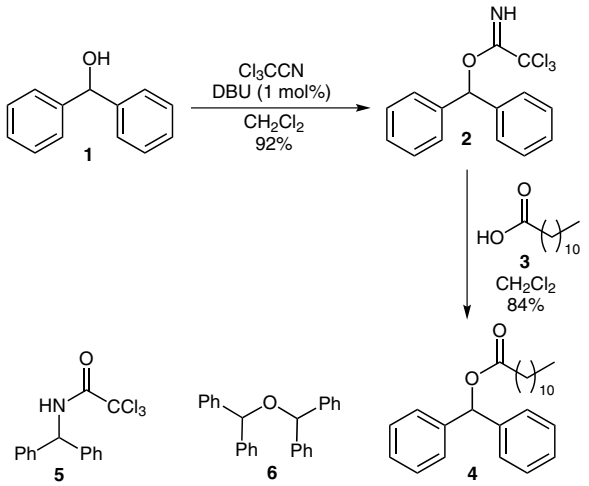
Formation of diphenylmethyl esters with simple substrates is typically effected using acid catalysis with diphenylmethanol,[5] however, these conditions do not tolerate complex substrates with delicate functionality. With sensitive substrates, diphenylmethyl esters are typically prepared by exposing the carboxylic acid to diphenyldiazomethane.[6] The unstable and toxic nature of this reagent[7] has led to a number of surrogate reactions based on the in situ formation of diphenyldiazomethane from diphenylmethyl hydrazone. Unfortunately, these procedures typically depend on strong oxidizing reagents or environmentally hazardous metal salts.[3b,7a,8] The scope of these esterifications is also restricted due to the powerful oxidizing conditions required to form the diphenyldiazomethane. Given the limitations associated with known methods, especially with carboxylic acids possessing sensitive functionality, esterification reagents that show improved convenience, practicality and safety are desirable. Ideally, any new reagent for the generation of diphenylmethyl esters would: 1) form the ester under mild conditions at room temperature, 2) not require stoichiometric amounts of toxic metal salts or powerful oxidizing agents, 3) react selectively with the carboxylic acid without disturbing other functionality in the molecule, and 4) be relatively stable with a long shelf-life.

Recently, we began to evaluate alternatives for the formation of diphenylmethyl esters under mild conditions from the corresponding trichloroacetimidate. Trichloroacetimidates are excellent alkylating agents under acidic conditions, as the alkylation is driven by the loss of the imidate and the formation of trichloroacetamide. This process provides a substantial thermodynamic driving force, facilitating the alkylation reactions. Most trichloroacetimidates require an acid catalyst to react with carboxylic acids and form esters,[9] however, there have been reports of spontaneous esterification with glycosyl imidates,[10] 4-methoxybenzyl trichloroacetimidate,[11] and 2-phenylisopropyl trichloroacetimidate.[12] In the spontaneous cases the imidate appears to act as a precursor to a stabilized carbocation. As the diphenylmethyl imidate can provide a similar stabilized carbocation, we hypothesized that the diphenylmethyl imidate may also function as an effective esterification reagent. The diphenylmethyl imidate is also a white solid, which should provide a greater shelf-life than 4-methoxybenzyl trichloroacetimidate and 2-phenylisopropyl trichloroacetimidate, which are both oils that undergo hydrolysis under ambient conditions.

To test these hypotheses, diphenylmethyl trichloroacetimidate (**2**) was prepared according to the procedure of Schmidt.[13] This reagent has been previously utilized in Lewis acid catalyzed etherification reactions to protect alcohols. Treatment of the commercially available and inexpensive diphenylmethanol (**1**) with trichloroacetonitrile and catalytic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded imidate **2** in 92% yield (Scheme 1). Purification of imidate **2** was performed using silica gel chromatography with 1% triethylamine as a co-solvent, as silica gel was acidic enough to facilitate decomposition of the imidate.

Initial studies on esterification with imidate **2** employed lauric acid (**3**) (Scheme 1). Simply mixing imidate **2** with lauric acid (**3**) in anhydrous dichloromethane provided the corresponding diphenylmethyl ester **4** in high conversion.

SYNLETT 2014, 25, 0283–0287
Advanced online publication: 03.12.2013
DOI: 10.1055/s-0033-1340293; Art ID: ST-2013-S0967-L



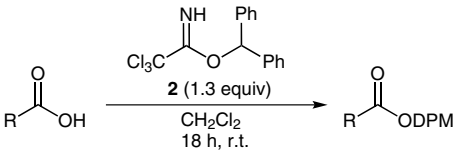
Scheme 1 Esterification of lauric acid (**3**) with imidate **2**

While the ester could be easily separated from trichloroacetamide, two other side products were also detected after purification, acetamide **5** and ether **6**. These compounds co-eluted with the ester product, which made purification significantly more difficult. The formation of ether **6** and acetamide **5** were traced to the use of an aqueous work-up and application of the reaction residue containing unreacted imidate **2** to silica gel without using triethylamine to buffer the purification medium. To facilitate isolation of the ester and to avoid the side products related to unreacted **2**, the aqueous work-up was omitted and the reaction mixture was purified directly by silica gel chromatography in the presence of triethylamine. This procedure provided pure ester **4** in 84% isolated yield without generating **5** and **6**.

The stability of pure diphenylmethyl trichloroacetimidate (**2**) as a solid is quite notable. Unlike 4-methoxybenzyl trichloroacetimidate and 2-phenylisopropyl trichloroacetimidate, which are oils that are prone to hydrolysis, imidate **2** is stable for at least several months when stored as a solid below 0 °C. During our work described herein, we did note that improper storage at room temperature over several weeks led to contamination of a sample of imidate **2** with acetamide **5**, which evidently forms from a thermally driven process. Experimentation showed that the rearrangement between imidate **2** and acetamide **5** was quite facile, with complete rearrangement being observed by simply heating imidate **2** in refluxing toluene for 24 hours without the addition of a catalyst. Still, with proper storage at low temperature, imidate **2** is stable for long periods making it a useful precursor to diphenylmethyl esters.

The scope of the esterification reaction was then investigated with a number of simple carboxylic acids (Table 1). These reactions were carried out by stirring the acids with 1.3 equivalents of imidate **2** in anhydrous dichloromethane at room temperature for 18 hours. Esterification of most substrates occurred in good to excellent yields. Simple alkyl acids reacted with **2** cleanly, to give the corresponding esters in 76–92% yields. Steric factors seemed to play a role with carboxylic acids bearing α-quaternary carbon centers (Table 1, entries 5 and 6), providing more moderate yields. Unsaturated carboxylic acids and aromatic acids also proved to be excellent substrates, affording the corresponding diphenylmethyl esters in high yields.

Table 1 Esterification Reactions with Diphenylmethyl Imidate **2**



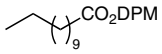
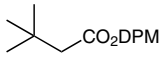
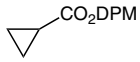
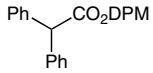
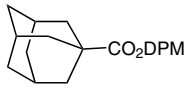
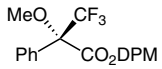
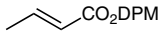
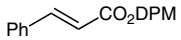
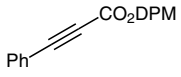
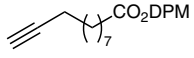
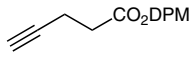
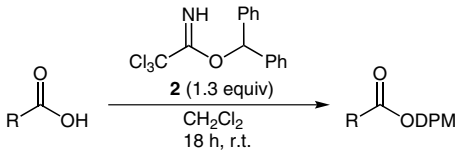
Entry	Ester	Yield (%)
1	 **4**	84
2	 **7**	92
3	 **8**	89
4	 **9**	76
5	 **10**	59
6	 **11**	59
7	 **12**	79
8	 **13**	93
9	 **14**	85
10	 **15**	79
11	 **16**	88
12	$PhCO_2DPM$ **17**	99

Table 1 Esterification Reactions with Diphenylmethyl Imidate **2** (continued)



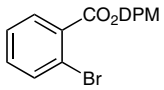
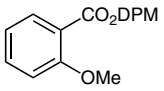
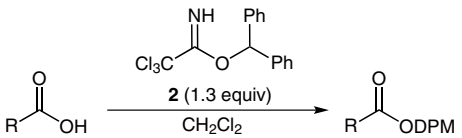
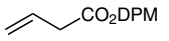
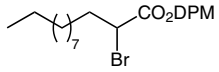
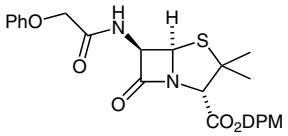
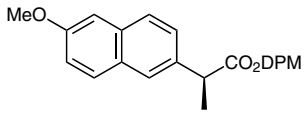
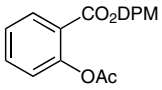
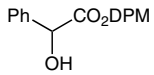
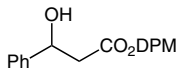
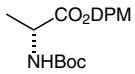
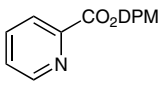
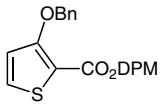
Entry	Ester	Yield (%)
13	 **18**	97
14	 **19**	74

Table 2 Esterification Reactions Using Imidate **2** with Complex Substrates

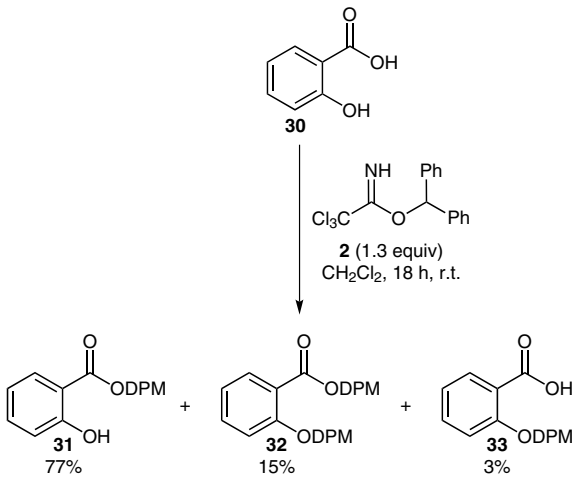


Entry	Ester	Yield (%)
1	 **20**	76
2	 **21**	83
3	 **22**	63
4	 **23**	89
5	 **24**	90
6	 **25**	92
7	 **26**	79
8	 **27**	76
9	 **28**	71
10	 **29**	75

In order to evaluate the utility of this new method in the presence of substrates possessing more sensitive functionalities, several complex carboxylic acids were explored (Table 2). Esterification of vinyl acetic acid provided ester **20** with only a trace amount of the product resulting from isomerization of the alkene into conjugation with the ester (~3% by ^{1}H NMR). Esterification was successful in the presence of both the α-bromide of **21** and the sensitive β-lactam ring of **22**, although the yield for **22** was moderate, likely due to steric considerations. No epimerization of the ester or opening of the β-lactam ring were detected for ester **22**, clearly demonstrating the esterification in a highly complex substrate. (*S*)-6-Methoxy-α-methyl-2-naphthaleneacetic acid (Table 2, entry 4) was chosen as a substrate, due to the highly enolizable stereogenic center adjacent to the carboxylic acid. No racemization was observed by chiral HPLC analysis after isolation of the corresponding diphenylmethyl ester **23**.

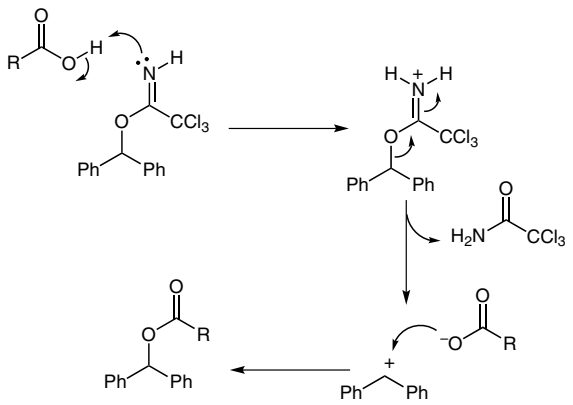
Other base-sensitive functionality such as the acetate ester of a phenol (as in ester **24**) was also stable to the reaction conditions. Esterification reactions with diphenylmethyl imidate **2** in the presence of protic functionality were also evaluated. Esterification of mandelic acid (Table 2, entry 6) showed that the presence of an unprotected alcohol was well tolerated. In addition, β-hydroxy ester **26** was formed in 79% yield without competing β-elimination or retroaldol reactions being observed. *tert*-Butoxycarbonyl-protected D-alanine was also esterified in good yield (Table 2, entry 8) using these reaction conditions. Again, no racemization of the adjacent stereogenic center was detected in ester **27** by chiral HPLC analysis. Attempts to esterify unprotected alanine were unsuccessful due to a lack of solubility of the zwitterion in dichloromethane, with no reaction being observed in more polar solvents such as *N*,*N*-dimethylformamide or acetonitrile.

Esterification of salicylic acid (**30**) under these conditions led to a mixture of products (Scheme 2). These included the ester **31**, the bis-protected salicylate **32** and a trace of the protected phenol **33**. The greater reactivity of the phenol evidently leads to some alkylation with the imidate, which was not observed with alcohols (e.g., **25** and **26**, Table 2).



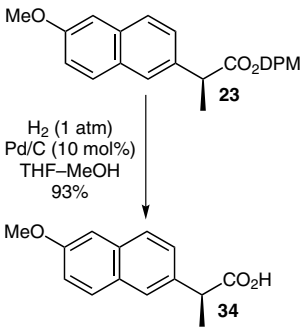
Scheme 2 Reaction of salicylic acid (**30**) with imidate **2**

Work in our laboratory and by others[10–12] has indicated that the spontaneous reaction of trichloroacetimidates with carboxylic acids occurs only when the imidates are precursors to stabilized carbocations. This observation suggests that these esterification reactions proceed through an S_N1 mechanism where the carboxylic acid is sufficiently acidic to initiate the reaction by protonation of diphenylmethyl imidate **2** (Scheme 3). Loss of trichloroacetamide then provides the diphenylmethyl cation, which is trapped by the carboxylate leading to the observed ester product. Support for this mechanism comes from the attempted esterification of *trans*-cinnamic acid in the presence of two equivalents of triethylamine. No esterification was observed under these conditions; instead the carboxylic acid was obtained unchanged. This suggests that the free carboxylic acid is acidic enough to promote the transformation and that the necessary pK_a of the initiating acid must lie below that of triethylammonium (10.75). The maximum pK_a of the initiating acid must also be higher than the pK_a of the pyridinium salt of 2-picolinic acid (5.39), as this ester was readily formed without an added acid (Table 2, entry 9), which would be impossible unless the pyridinium salt can protonate the imidate and initiate the reaction.



Scheme 3 Proposed mechanism of the esterification

Cleavage of the highly enolizable ester **23** back to the acid without racemization was also briefly investigated. Hydrogenation was chosen for this deprotection, as removal of diphenylmethyl esters via this process has been reported to proceed at accelerated rates compared to other functionalized benzyl esters.[1b] Submitting naproxen ester **23** to standard hydrogenation conditions with palladium on carbon led to the formation of the free carboxylic acid **34** in 93% yield without racemization of the α-stereocenter (Scheme 4).



Scheme 4 Deprotection of diphenylmethyl ester **23** without racemization

In summary, a convenient method for the protection of carboxylic acids as their diphenylmethyl esters has been reported.[14,15] The use of the diphenylmethyl imidate **2** allows for formation of diphenylmethyl esters without relying on toxic and energetic diazo reagents. In addition, no strong oxidizing agents or toxic metal salts are needed for this new esterification. The required imidate reagent is easily prepared from inexpensive starting materials and can be used to esterify efficiently a variety of carboxylic acid substrates. These esterifications are operationally simple and proceed without the requirement of any Brønsted or Lewis acid. The conditions for the esterification are quite mild, and do not disturb stereogenic centers adjacent to the reacting carboxylic acid or other sensitive functional groups. In addition, this esterification is tolerant of unprotected alcohols, carbamates and nitrogen heterocycles. Imidate **2** also displayed a long shelf-life when stored at low temperature. Given the continuing need for convenient, safe, inexpensive and tolerant esterification reagents,[16] diphenylmethyl imidate **2** should find application for the protection of complex carboxylic acids where mild reaction conditions are essential.

Acknowledgment

Acknowledgement is made to Syracuse University for support of this research.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, **2006**, 4th ed., 604. (b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, **2005**, 3rd ed. 414.

(2) (a) Zhou, H.; van der Donk, W. *Org. Lett.* **2002**, *4*, 1335. (b) Baldwin, J. E.; Adlington, R. M.; Crouch, N. P.; Schofield, C. J.; Turner, N. J.; Aplin, R. T. *Tetrahedron* **1991**, *47*, 9881.

(3) (a) Micetich, R. G.; Maiti, S. N.; Spevak, P. *Synthesis* **1986**, 292. (b) Bywood, R.; Gallagher, G.; Sharma, G. K.; Walker, D. *J. Chem. Soc., Perkin Trans. 1* **1975**, *20*, 2019. (c) Kametani, T.; Sekine, H.; Honda, T. *Chem. Pharm. Bull.* **1982**, *30*, 4545.

(4) (a) Matsuura, F.; Hao, J.; Reents, R.; Kishi, Y. *Org. Lett.* **2006**, *8*, 3327. (b) Hale, K. J.; Lazarides, L.; Cai, J. *Org. Lett.* **2001**, *3*, 2927. (c) Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1985**, *50*, 470. (d) Valentekovich, R. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 9069. (e) Vyas, D. M.; Skonezny, P. M.; Jenks, T. A.; Doyle, T. W. *Tetrahedron Lett.* **1986**, *27*, 3099. (f) Hoppe, D.; Schmincke, H.; Kleemann, H. W. *Tetrahedron* **1989**, *45*, 687. (g) Bates, R. W.; Fernandez-Megia, E.; Ley, S. V.; Ruck-Braun, K.; Tilbrook, D. M. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1917. (h) Xu, Z.; Peng, Y.; Ye, T. *Org. Lett.* **2003**, *5*, 2821. (i) Matsuura, F.; Peters, R.; Anada, M.; Harried, S. S.; Hao, J.; Kishi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 7463.

(5) Paredes, R.; Agudelo, F.; Taborda, G. *Tetrahedron Lett.* **1996**, *37*, 1965.

(6) Lapatsanis, L.; Milias, G.; Paraskewas, S. *Synthesis* **1985**, 513.

(7) (a) Javed, M. I.; Brewer, M. *Org. Synth.* **2008**, *85*, 189. (b) Sammakia, T. *Diphenyldiazomethane*, In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, **2001**, 2209.

(8) Curini, M.; Rosati, O.; Pisani, E.; Cabri, W.; Brusco, S.; Riscazzi, M. *Tetrahedron Lett.* **1997**, *38*, 1239.

(9) (a) Kokotos, G.; Chiou, A. *Synthesis* **1997**, 168. (b) Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483.

(10) (a) Schmidt, R. R.; Michel, J. *Angew. Chem.* **1980**, *92*, 763. (b) Schmidt, R. R.; Michel, J. *J. Carbohydr. Chem.* **1985**, *4*, 141.

(11) (a) Shoji, M.; Uno, T.; Hayashi, Y. *Org. Lett.* **2004**, *6*, 4535. (b) Shoji, M.; Uno, T.; Kakeya, H.; Onose, R.; Shiina, I.; Osada, H.; Hayashi, Y. *J. Org. Chem.* **2005**, *70*, 9905.

(12) (a) Thierry, J.; Yue, C.; Potier, P. *Tetrahedron Lett.* **1998**, *39*, 1557. (b) Respondek, T.; Cueny, E.; Kodanko, J. J. *Org. Lett.* **2012**, *14*, 150.

(13) Ali, I. A. I.; El Ashry, E. S. H.; Schmidt, R. R. *Eur. J. Org. Chem.* **2003**, 4121.

(14) **Diphenylmethyl Cinnamate (13);**[15] **Typical Procedure**
Cinnamic acid (0.200 g, 1.35 mmol) and diphenylmethyl trichloroacetimidate (**2**) (0.580 g, 1.76 mmol) were added to a flame-dried round-bottom flask. Anhydrous CH_2Cl_2 (5.4 mL) was then added and the mixture was stirred under Ar for 18 h. Et_3N (0.5 mL) was added and the mixture was adsorbed onto silica gel. Purification by silica gel chromatography (Et_3N–EtOAc–hexanes, 1:5:94) provided diphenylmethyl cinnamate (**13**) (0.400 g, 93%) as a white solid.
Mp 74–77 °C; R_f = 0.57 (EtOAc–hexanes, 10:90). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 16.2 Hz, 1 H), 7.57–7.54 (m, 2 H), 7.44–7.26 (m, 13 H), 7.05 (s, 1 H), 6.58 (d, *J* = 15.9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 145.7, 140.5, 134.5, 130.7, 129.1, 128.8, 128.4, 128.2, 127.4, 118.2, 77.2.

(15) Compound **13** has been previously prepared, see: Magens, S.; Plietker, B. *J. Org. Chem.* **2010**, *75*, 3715.

(16) (a) Tummatorn, J.; Albiniak, P. A.; Dudley, G. B. *J. Org. Chem.* **2007**, *72*, 8962. (b) Lopez, S. S.; Dudley, G. B. *Beilstein J. Org. Chem.* **2008**, *4*, No. 44. (c) Heller, S. T.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4572. (d) Twibanire, J.-d'A. K.; Grindley, T. B. *Org. Lett.* **2011**, *13*, 2988.