Organic & Biomolecular Chemistry

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Cite this: DOI: 10.1039/c5ob02455b

Formation of DPM ethers using *O*-diphenylmethyl trichloroacetimidate under thermal conditions†

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Received 1st December 2015,
Accepted 16th December 2015

DOI: 10.1039/c5ob02455b

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Alcohols are effectively converted to their corresponding diphenylmethyl (DPM) ethers by reaction with *O*-diphenylmethyl trichloroacetimidate in refluxing toluene without the requirement of a catalyst or other additives. A number of acid and base sensitive substrates were protected in excellent yield using this new method without disturbing the pre-existing functionality present in these molecules. This reaction is the first example of the formation of an ether from stoichiometric amounts of a trichloroacetimidate and an alcohol without the addition of a Brønsted or Lewis acid catalyst.

Introduction

Diphenylmethyl (DPM) ethers (also known as benzhydryl ethers) are commonly employed as protecting groups for alcohols.[1] DPM ethers may be cleaved either by hydrogenation[2] (making them a good surrogate for benzyl ethers) or under acidic conditions[3] (where they can substitute for PMB or MOM ethers). This flexibility in the removal of DPM ethers is especially beneficial in complex molecules containing delicate functionality where it can be difficult to predict the best means of deprotection *a priori*. The large size of the DPM ether has also been proven advantageous in some enantioselective transformations where the bulk provided by the DPM ether provides a steric bias, increasing the selectivity in certain substrates.[4] The DPM ether has also been employed in medicinal chemistry to incorporate a large hydrophobic group into biologically active molecules, increasing the lipophilicity.[5]

Typically DPM ethers are formed under acidic conditions from benzhydryl alcohol using protic or Lewis acids.[3] These conditions are often harsh, and usually require high acid catalyst loadings and elevated temperatures.[6] Metal catalysts such as palladium(II) chloride[7] and gold(I) salts[8] have also been used to install DPM ethers under more mild conditions, with the caveat that these catalysts are more expensive. Attempts to find more mild reaction conditions to form DPM ethers have led to the use of diphenyldiazomethane.[9] While these conditions are quite mild, diazo compounds are inherently unstable, typically requiring fresh preparation for good yields. In addition, given the high toxicity and shock sensitive nature of diazo compounds,[10] care must be taken in their use, especially on a large scale.

Schmidt and co-workers have previously described the synthesis of *O*-diphenylmethyl trichloroacetimidate, which was employed in the synthesis of DPM ethers.[11] Traditionally trichloroacetimidates have been used to protect alcohols as ethers by utilizing Brønsted or Lewis acid catalysts,[12] with the DPM ethers being no exception, providing excellent yields under mild conditions when a catalytic amount of TMSOTf was employed. These conditions may be problematic for acid-sensitive substrates, however. For example, etherification of β-trimethylsilylethanol has been reported to be incompatible with acidic trichloroacetimidate protection conditions.[13] The development of new imidate-based reagents has been an active field, with similar systems based on a triazine scaffold having recently been introduced for the introduction of benzyl[14] and PMB ethers.[15] New trifluoroacetimidate[16] and phosphinimidate-based[17] reagents for etherification have also been advanced, however, all these systems require activation with TMSOTf or another acid catalyst.

Of late there has been a surge of research activity in the development of new reagents for the protection of alcohols as substituted benzyl ethers under mild conditions that do not disturb any sensitive functionality in complex molecules. Exemplifying these reagents, Dudley has reported the benzylation of alcohols using benzyloxy pyridinium triflates in refluxing α,α,α-trifluorotoluene.[13,18] Similar systems have also been developed for the formation of PMB ethers utilizing a lepidine derivative as the benzyl transfer reagent.[19] The quaternary pyridinium salts may also be generated *in situ* by the addition of methyl triflate to an appropriately functionalized pyridine or quinoline system.[19b,20] Recent additions to these reagents include triazinylammonium salts developed by the Kunishima group which install benzyl ethers at room temperature.[21] Both

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†Electronic supplementary information (ESI) available: Full experimental details, tabulated characterization data, ^{1}H and ^{13}C NMR spectra, and chiral HPLC traces. See DOI: 10.1039/c5ob02455b

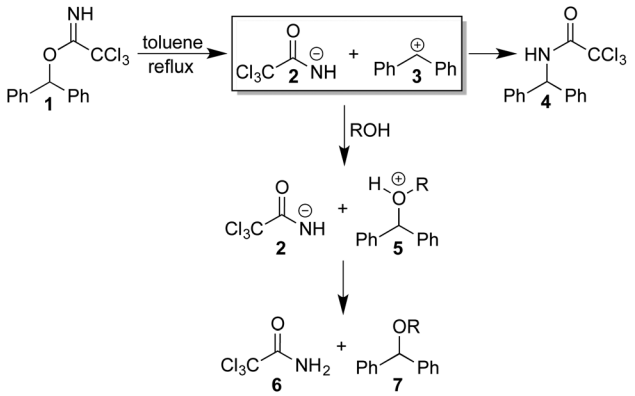


Fig. 1 Intercepting the DPM cation with an alcohol.

the Dudley and Kunishima systems function optimally with the addition of an additive such as MgO, which functions as a mild base and a desiccant to scavenge adventitious acid and/or trace amounts of water.

Our recent experiences with the reactivity of trichloroacetimidates in the formation of esters[22] and sulfides[23] without an added catalyst led us to consider the direct formation of ethers from an alcohol and a trichloroacetimidate without the use of any additive. In our earlier studies[22a] we have noted that DPM imidate **1** would rearrange to the corresponding acetamide **4** when heated in refluxing toluene (Fig. 1). Allylic trichloroacetimidates are known to rearrange through a concerted [3,3]-sigmatropic rearrangement (the Overman rearrangement[24]), but this mechanism is not available to imidate **1**. There have been previous reports of benzylic imidates undergoing rearrangement in the presence of a strong acid,[25] likely through a cationic pathway. Due to the stability of the diphenylmethyl cation, we therefore hypothesized that the imidate ionizes under thermal conditions to form the cation **3** and the trichloroacetamide anion **2**, a weak base and a poor nucleophile. Should no competing nucleophile be present, the trichloroacetamide anion adds to the cation and the corresponding acetamide **4** is formed. However, in the presence of an external nucleophile like an alcohol, we reasoned that it may be possible to intercept cation **3**, leading to the direct formation of ether **7** and trichloroacetamide **6**. A search of the literature found a single example of the uncatalyzed formation of an ether from a trichloroacetimidate reported by Schmidt and coworkers.[26] This reaction involved the solvolysis of an *O*-glucopyranosyl trichloroacetimidate with methanol. Attempts to displace the same imidate with more complex alcohols were reported to provide no ether products under similar solvolysis conditions.

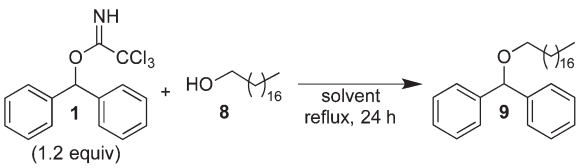
Results and discussion

The more reactive DPM imidate **1** may be able to capture a stoichiometric amount of an alcohol nucleophile to form the corresponding DPM ether (Fig. 1). This reaction would provide a mild entry into DPM ethers under near neutral conditions, where the strongest base present is the trichloroacetamide anion (the pK_a of trichloroacetamide has been reported as 11.2 (ref. 27)). Furthermore, DPM trichloroacetimidate **1** is a white solid that is easy to handle and can be stored for long periods of time (several months in a refrigerator[22a]) without decomposition. Therefore imidate **1** has many of the elements desired in an excellent etherification reagent. Given its high reactivity, DPM imidate **1** was chosen as a test case for additive-free ether formation, with some exploratory reaction screening performed to determine the viability of the process.

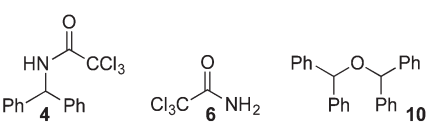
Initial experiments were conducted with 1-octadecanol **8**. When alcohol **8** and 1.2 equivalents of imidate **1** were dissolved in toluene and heated to 50 °C for 24 hours, a 24% yield of the desired ether **9** along with a significant amount of unreacted starting materials was obtained. Warming the reaction to reflux in toluene led to a more useful 85% isolated yield. Other solvents were less effective, even when heated to temperatures near that of refluxing toluene (1,4-dioxane, α,α,α-trifluorotoluene, DMF). Removal of the trichloroacetamide by-product **6** from the nonpolar ether product **9** was accomplished by washing the crude reaction mixture with aqueous 2 M sodium hydroxide solution, greatly facilitating purification. As needed, additional purification by chromatography removed trace amounts of the dimeric DPM ether **10** and, occasionally, small amounts of trichloroacetamide **4** (Table 1).

With the conditions in hand, a number of simple substrates were tested in this new etherification process (Table 2). The reaction proceeded very well for primary benzyl alcohols as

Table 1 Etherification with imidate **1** under thermal conditions

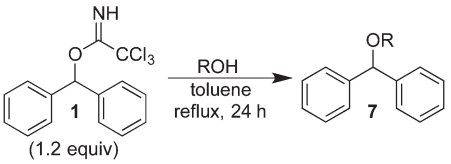


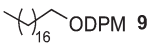
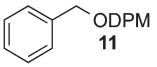
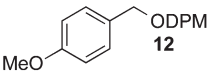
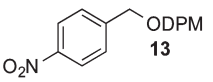
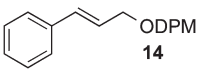
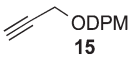
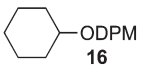
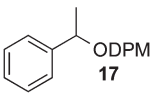
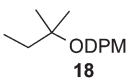
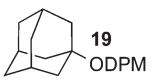
Entry	Solvent	Temperature	Yield[a]
1	Toluene	50 °C	24%
2	Toluene	111 °C	85%
3	α,α,α-Trifluorotoluene	102 °C	62%
4	1,2-Dichloroethane	83 °C	66%
5	Dichloromethane	40 °C	18%
6	THF	66 °C	36%
7	1,4-Dioxane	101 °C	60%
8	Acetonitrile	82 °C	28%
9	DMF	110 °C	33%



[a] Isolated yield.

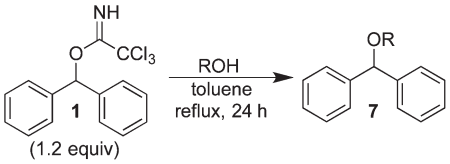
Table 2 Etherification of simple alcohols using DPM imidate **1**

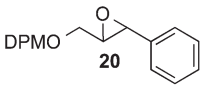
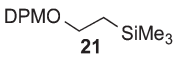
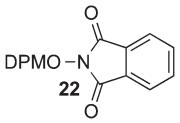
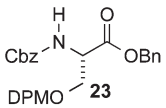
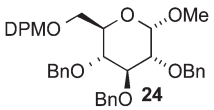
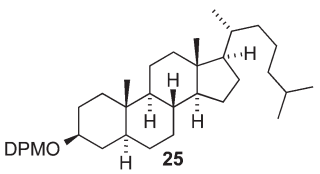
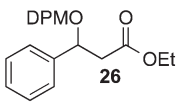
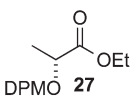
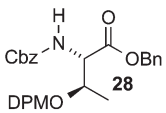
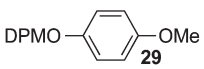
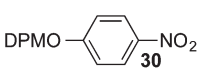
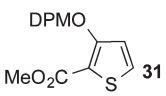


Entry	DPM ether	Yield[a]
1		85%
2		94%
3		71%
4		88%
5		88%
6		97%
7		93%
8		92%
9		85%
10		92%

[a] Isolated yield.

Table 3 Etherification of complex alcohols and phenols using DPM imidate **1**

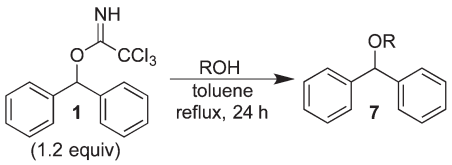


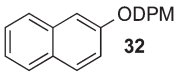
Entry	DPM ether	Yield[a]
1		65%
2		79%
3		80%
4		91%[b]
5		73%
6		80%
7		96%
8		90%
9		84%[b]
10		91%
11		61%
12		53%

shown in entries 2–4 (Table 2). Interestingly cinnamyl alcohol (entry 5), which is a challenging substrate for some etherification reagents,[18d] gave an 88% yield of the corresponding ether **14**. Propargyl alcohol also proved to be an excellent substrate, and gave the corresponding ether **15** in 97% yield. Simple secondary alcohols were also successively etherified with DPM imidate as shown in entries 7 and 8 (Table 2). Entries 9 and 10 demonstrate that tertiary alcohols may be protected with DPM imidate in high yields.

In addition to the simple substrates shown in Table 2, a number of more complex examples were subjected to the etherification conditions with DPM imidate **1** (Table 3). Sensitive substrates like the epoxide containing ether **20** were successfully formed in good yields (entry 1, Table 3). Etherifi-

Table 3 *(Contd.)*



Entry	DPM ether	Yield[a]
13		74%

[a] Isolated yield. [b] The reaction was allowed to proceed for 48 hours, and a second equiv. of DPM imidate was added after 24 h.

cation of β-trimethylsilylethanol was also readily accomplished (entry 2, Table 3) in 79% yield. This result is notable as protection of β-silyl alcohols is complicated by rapid Peterson elimination[28] under acidic or basic conditions, complicating the etherification. As discussed above, the protection of β-trimethylsilylethanol has been reported to be incompatible with acid-catalyzed imidate etherification reactions.[13] The base sensitive *N*-hydroxyphthalimide also provided a high yield of the DPM ether **22**. Other sensitive substrates also performed well, resulting in the formation of β-alkoxyester **26** and α-alkoxyester **27** in yields of 96% and 90% respectively.

No racemization was observed in the formation of serine ether **23**, lactate DPM ether **27** or threonine ether **28** as determined by chiral HPLC (for **23** and **27**) and ^{1}H NMR analysis (**28**). A number of phenol and phenol-like substrates were also etherified with this methodology (entries 10–13, Table 3). These reactions demonstrate that DPM ethers can be formed under neutral conditions in the presence of a sensitive functionality utilizing only the DPM trichloroacetimidate.

Conclusions

In summary, a mild method for protecting primary, secondary and tertiary alcohols in high yields using diphenylmethyl trichloroacetimidate **1** under thermal conditions has been demonstrated. In contrast to other conditions more commonly advanced, these thermal protection conditions do not require the use of an acid catalyst or other additives. Indeed, this study is the first report of the etherification of an alcohol utilizing a stoichiometric amount of a trichloroacetimidate that proceeds without the addition of an acid catalyst or a promoter. The DPM ethers may be formed in high yields in systems containing both acid and base sensitive functionalities. These mild reaction conditions have shown compatibility with polyfunctional molecules, and the necessary reagents may be accessed from simple, inexpensive starting materials. In addition, the DPM imidate reagent **1** is quite stable, and can be stored for long periods of time in a refrigerator, making it easy to maintain a stock of the reagent. This procedure provides a general method for the protection of alcohols as DPM ethers, and should facilitate the protection of sensitive substrates and popularize the use of DPM ethers in synthetic applications.

Experimental section

Representative procedures for the formation of DPM ethers with DPM trichloroacetimidate (1) under thermal conditions

Octadecyloxydiphenylmethane (8). 1-Octadecanol (200 mg, 0.739 mmol) was placed in a flame dried round bottom flask and dissolved in anhydrous toluene to a concentration of 0.25 M (3 mL). Trichloroacetimidate **1** (291 mg, 0.887 mmol, 1.2 equiv.) was added and the reaction was warmed to reflux. After 18 hours, the reaction was allowed to cool to room temperature and concentrated under reduced pressure. The residue was pre-adsorbed on silica gel and purified by silica gel column chromatography (1% ethyl acetate/hexanes) to provide 0.273 g (85%) of octadecyloxydiphenylmethane (**8**) as a white solid. Mp = 47–48 °C; TLC R_f = 0.80 (10% ethyl acetate/hexanes); IR (thin film from CH_2Cl_2) 3027, 2923, 2852, 1493, 1453, 1097 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.37 (m, 10H), 5.33 (s, 1H), 3.44 (t, J = 6.6 Hz, 2H), 1.60–1.67 (m, 2H), 1.26 (m, 30H), 0.88 (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 128.5, 127.5, 127.2, 83.8, 69.4, 32.2, 30.1, 29.94, 29.91, 29.87, 29.85, 29.7, 29.6, 26.5, 22.9, 14.3 (several signals in the aliphatic region were not resolved). Anal calcd for $C_{31}H_{48}O$: C, 85.26; H, 11.08. Found: C, 85.18; H, 11.13.

1-(Benzhydryloxy)adamantane (19). 1-Adamantanol (200 mg, 1.313 mmol) was placed in a flame dried round bottom flask and dissolved in anhydrous toluene to a concentration of 0.25 M (5 mL). Trichloroacetimidate **1** (515 mg, 1.576 mmol, 1.2 equiv.) was added and the reaction was warmed to reflux. After 18 hours, the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was pre-adsorbed on silica gel and purified by silica gel column chromatography (1% ethyl acetate/hexanes) to provide 0.383 g (92%) of 1-(benzhydryloxy)adamantane (**19**) as an orange solid. Mp = 64–66 °C; TLC R_f = 0.71 (10% ethyl acetate/hexanes); IR (thin film from CH_2Cl_2) 3025, 2905, 2850, 1492, 1451, 1354, 1082 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.39 (m, 10H), 5.80 (s, 1H), 2.14 (s, 3H), 1.83 (bs, 6H), 1.62 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 128.2, 127.2, 126.9, 74.4, 73.8, 43.0, 36.6, 30.8. Anal calcd for $C_{23}H_{26}O$: C, 86.75; H, 8.23. Found: C, 86.72; H, 8.18.

(*S*)-Benzyl 3-(benzhydryloxy)-2-(((benzyloxy)carbonyl)amino) propanoate (23). *N*-Benzyloxycarbonyl-L-serine benzyl ester (200 mg, 0.607 mmol) was placed in a flame dried round bottom flask and dissolved in anhydrous toluene to a concentration of 0.25 M (2.5 mL). Trichloroacetimidate **1** (239 mg, 0.728 mmol, 1.2 equiv.) was added and the reaction was warmed to reflux. After 24 hours the reaction still showed the starting material by thin layer chromatography analysis, so more trichloroacetimidate **1** was added (239 mg, 0.728 mmol, 1.2 equiv.). After another 24 hours at reflux, the reaction was

allowed to cool to room temperature and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with 2 M aq. NaOH (3×), dried (Na_2SO_4) and concentrated (this workup removes the trichloroacetamide by-product). The residue was pre-adsorbed on silica gel and purified by silica gel column chromatography (15% ethyl acetate/hexanes) to provide 0.273 g (91%) of (*S*)-benzyl 3-(benzhydryloxy)-2-(((benzyloxy)carbonyl)amino) propanoate (**23**) as a clear oil. $[\alpha]_D^{21.6}$ −12.5 (*c* 1.26, $CHCl_3$); TLC R_f = 0.18 (10% ethyl acetate/hexanes); IR (thin film from CH_2Cl_2) 3434, 3341, 3062, 3030, 2949, 2876, 1722, 1498, 1339, 1197, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07–7.30 (m, 20H), 5.63 (d, J = 12.0 Hz, 1H), 5.19 (s, 1H), 5.12 (d, J = 4.0 Hz, 2H), 5.04 (s, 2H), 4.49 (dt, J = 2.8 Hz, 1H), 3.84 (dd, J = 9.4, 2.8 Hz, 1H), 3.60 (dd, J = 9.4, 3.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 156.1, 141.6, 141.4, 136.4, 135.4, 128.7, 128.65, 128.6, 128.5, 128.4, 128.3, 128.2, 127.7, 127.0, 126.9, 84.2, 69.0, 67.4, 67.2, 54.8 (two signals in the aromatic region were not resolved). Anal calcd for $C_{31}H_{29}NO_5$: C, 75.13; H, 5.90; N, 2.83. Found: C, 74.94; H, 5.97; N, 3.00. Chiral HPLC analysis: chiralcel OD (heptane/2-PrOH = 90/10, 1.0 mL min^{-1}, 254 nm, 25 °C): $t_{(S\ \text{enantiomer})}$ = 16.7 min, $t_{(R\ \text{enantiomer})}$ = 23.9 min.

Acknowledgements

Financial support was provided by the National Institute of General Medical Sciences (R15-GM116054). Acknowledgement is also made to the Donors of the American Chemical Society Petroleum Research Fund for a New Directions award in support of this research (54823-ND1). Support for the Syracuse University NMR facility used in this study was provided by the National Science Foundation (CHE-1229345), which is gratefully acknowledged.

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