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A carbon tetrachloride-free synthesis of *N*-phenyltrifluoroacetimidoyl chloride

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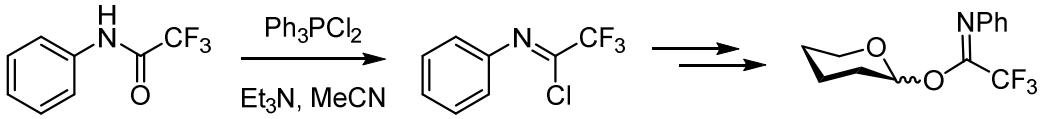
*Graphical abstract*



Note

# A carbon tetrachloride-free synthesis of *N*-phenyltrifluoroacetimidoyl chloride

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*Keywords*

Glycosylation; imidoyl chloride; green chemistry

*Abstract*

*N*-Phenyltrifluoroacetimidoyl chloride (PTFAI-Cl) is a reagent widely used for the preparation of glycosyl *N*-phenyltrifluoroacetimidates. However, the most commonly applied method requires carbon tetrachloride, a hepatotoxic reagent that has been phased out under the Montreal Protocol. We report a new synthesis of *N*-phenyltrifluoroacetimidoyl chloride (PTFAI-Cl) using dichlorotriphenylphosphane and triethylamine.

Glycosyl N-phenyltrifluoroacetimidates (PTFAI; Figure 1a) are a powerful class of glycosyl donors [1]. Since their first disclosure in 2001 [2], these glycosyl donors have rapidly risen to become a mainstay of carbohydrate chemistry. The two main benefits of PFTAI donors over the more commonly-applied trichloroacetimidates (TCAs) are (1) their greater stability, particularly for 2-deoxy sugars, and (2) the lower nucleophilicity of the released *N*-phenyltrifluoroacetamide versus trichloroacetamide. Thus, for example, PFTAI donors allow the high yielding glycosylation of the amide of asparagine, whereas for TCAI donors the trichloroacetamide by-product competes, lowering yields [3]. As well, comparison of a panel of deoxysugar PFTAI and TCAI donors led to the conclusion that the former were more stable, which led to higher yields of the glycosides [4].

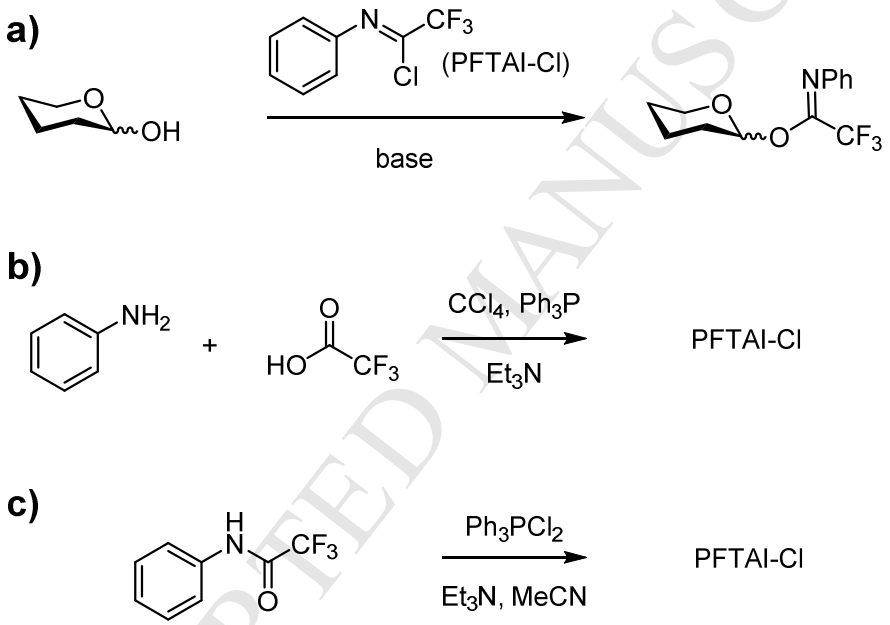


**Fig. 1.** a) Preparation of glycosyl *N*-phenyltrifluoroacetimidates (PFTAIs) using *N*-phenyltrifluoroacetimidoyl chloride (PTFAI-Cl). b) Prior approach to the synthesis of PFTAI-Cl using carbon tetrachloride [5]. c) This work.

Glycosyl PFTAIs are formed by the reaction of sugar hemiacetals with *N*-phenyltrifluoroacetimidoyl chloride (PTFAI-Cl) in the presence of a base (Figure 1a). The most common approach for synthesis of PTFAI-Cl involves refluxing aniline with trifluoroacetic acid, triphenylphosphine, and triethylamine in carbon tetrachloride, followed by distillation [5]. However, carbon tetrachloride is subject to the Montreal Protocol on Substances that Deplete the Ozone Layer, and has a tropospheric lifetime estimate of 35 years [6]. As a class I ozone-depleting substance, the phase-out target for carbon tetrachloride was

1996. Moreover carbon tetrachloride is a potent hepatotoxin [7]. PTFAI-Cl is commercially available; it is not known whether the commercial synthesis utilizes carbon tetrachloride. Accordingly, we sought to develop a carbon tetrachloride-free synthesis of PTFAI-Cl. Several carbon tetrachloride-free syntheses of PFTAI-Cl have been reported. An early approach to imidoyl chlorides involved treatment of amides with $PCl_5$; however, the yields were relatively low and were complicated by the formation of diazadiphosphetidines [8]. An approach involving $POCl_3$ required specialized equipment and high temperature [9]. A patent report discloses a synthesis of PTFAI-Cl by treatment of *N*-phenyltrifluoroacetamide with $(PhO)_2POCl/Et_3N$ [10].

The existing approach using $TFA/Ph_3P/Et_3N/CCl_4$ may be considered a variant of the Appel reaction, and likely proceeds via a $[Ph_3PCl]^+[CCl_3]^-$ intermediate [11]. Therefore we explored the use of other halogen donor compounds. Attempts to convert *N*-phenyltrifluoroacetamide to PTFAI-Cl using $Cl_3CCN/Ph_3P$ [12, 13] or thionyl chloride [14] using the literature methods were unsuccessful. Our preferred method, reported below, involves the treatment of *N*-phenyltrifluoroacetamide with $Ph_3PCl_2/Et_3N$ [11]. PFTAI-Cl is relatively stable and can be purified by flash chromatography and is sufficient for use in standard protocols for preparation of glycosyl PFTAIs. We also note that various benzyl and allyl PFTAI derivatives are of utility in the acid-catalyzed etherifications [15-17], and this new approach should support the environmentally-friendly synthesis of these reagents.

***Experimental***

Note: Like carbon tetrachloride, dichlorotriphenylphosphorane ($Ph_3PCl_2$) is classified as an IARC Group 2B substance (possibly carcinogenic to humans).

**_N_-Phenyl-2,2,2-trifluoroacetimidoyl chloride (PFTAI-Cl)**

*N*-Phenyltrifluoroacetamide [18] (4.00 g, 21.2 mmol) and dichlorotriphenylphosphorane (17.6 g, 52.9 mmol) were suspended in MeCN (80 ml) and $Et_3N$ (7.67 ml, 55.0 mmol) was added. The suspension was refluxed for 3 h and then cooled to 0 °C. The precipitated solids ($Et_3N.HCl$ and $Ph_3PO$) were removed by filtration and the filtrate concentrated under reduced pressure. The residue was dissolved in minimal $CHCl_3$ and triturated with hexanes. The precipitate was removed by filtration and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography ($Et_2O$/hexanes 1:4) afford the chloride as a

colourless liquid (2.68 g, 61%). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.48–7.40 (m, 2H), 7.34–7.28 (m, 1H), 7.13–7.07 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 143.6, 132.1 (q, *J* 277.1), 129.3, 127.6, 120.8, 117.0 (q, *J* 43.0); IR (acetone) 1506, 1260, 1093, 1055, 1012, 795, 693; HRMS (Orbitrap) calcd for $C_8H_5ClF_3N$ $[M+H]^+$ 208.0135, found 208.0136.

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*Highlights*

- *N*-Phenyltrifluoroacetimidoyl chloride (PTFAI-Cl) is used in the synthesis of glycosyl *N*-phenyltrifluoroacetimidates.
- A new synthesis of *N*-phenyltrifluoroacetimidoyl chloride (PTFAI-Cl) is reported.
- The method avoids the use of ozone-depleting and hepatotoxic carbon tetrachloride.