

SYNLETT
Spotlight 1992,2,2-Trichloroethyl Chloroformate
(TrocCl)

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This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Ederson Oliveira dos Reis was born in Rio de Janeiro, Brazil in 1979. He obtained his M.Sc. in organic chemistry from Federal University of Rio de Janeiro in 2005. Earlier, he graduated in pharmacy and in chemistry from Federal University of Rio de Janeiro and Rio de Janeiro State University. Currently he is working towards his Ph.D. in organic chemistry under the supervision of Prof. Débora de Almeida Azevedo and D.Sc. Adriana Farah. His research interests are focused on the synthesis of different quinic acid derivatives such as chlorogenic acids and their lactones.

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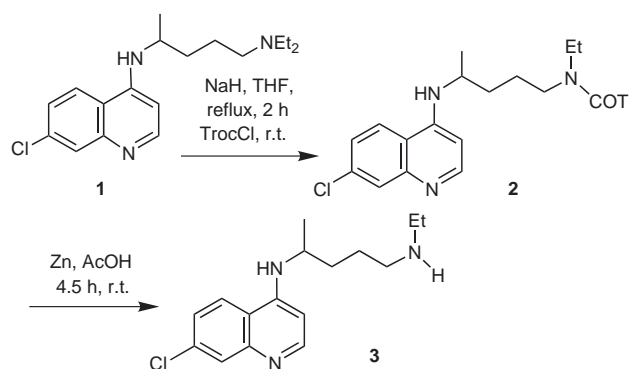
Introduction

2,2,2-Trichloroethyl chloroformate (TrocCl, $\text{CCl}_3\text{CH}_2\text{OCOCl}$, bp 171–172 °C) is a stable chloroformate which acylates aliphatic and aromatic hydroxyl and amino groups under mild conditions.^{1,2} This reagent is commercially available and has been widely used in regio-, chemo-, and stereoselective syntheses. The Troc group shows a sharp and characteristic proton singlet at $\delta = 4.68\text{--}4.89$ ppm, which makes its presence or absence easily detectable by ^1H NMR spectroscopy.^{3–5} TrocCl has

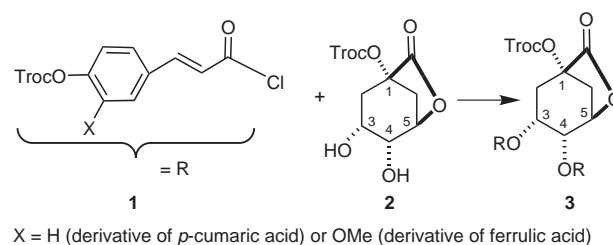
proved to be an excellent reagent for dealkylation of secondary or tertiary amines, with good selectivity, thus producing clean reaction products.^{1,3} Moreover, TrocCl is a suitable substrate for Mitsunobu inversion reactions.⁶ Recently, the total synthesis of Aprotaxin A with protection and deprotection of an allyl ester intermediate with TrocCl was described.⁷ Several methods of Troc removal have been described, leaving a wide variety of other functional groups unaffected.^{7,8,10} The following examples highlight the importance and early applicability of this reagent in organic chemistry.

Abstracts

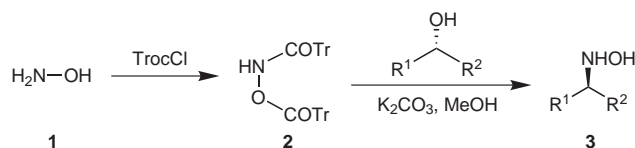
(A) Ansari and Craig³ have described the use of TrocCl to achieve desethylchloroquine (**3**) in a short, efficient two-step synthesis. In the first step, an internal amide ion from the secondary nitrogen in chloroquine (**1**) is generated, followed by rapid elimination of an ethyl group. The carbamate **2** thus produced easily undergoes deprotection to the target compound at room temperature with zinc in acetic acid.



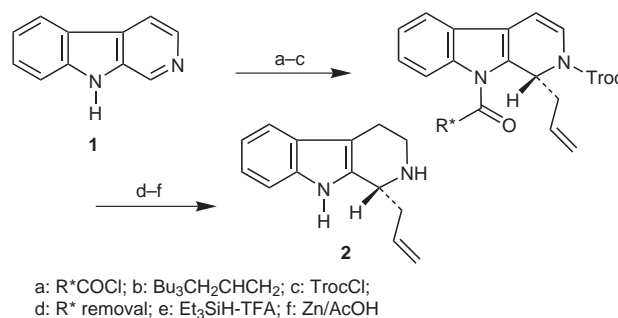
(B) TrocCl selectively acylates the aromatic hydroxyl group of ferrulic and *p*-cumaric acids (**1**). TrocCl is also used to protect the C-1 position of 3,4-isopropylidene-1,5-quinide (**2**) in the preparation of 3,4-disubstituted lactones **3**. It was shown that the use of TrocCl provides for regiospecificity of the esterification and impedes any degradation or isomerization.^{4,11}



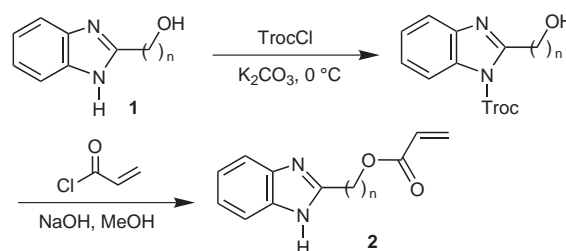
(C) Hydroxylamines **2** that are doubly N,O-protected with Troc are easily obtained from TrocCl and hydroxylamine (**1**). According to Knight and Leese,⁶ these intermediates allow ready access to enantiopure hydroxylamines **3** starting from the corresponding secondary alcohols.



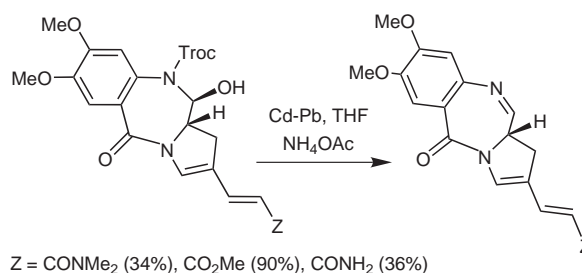
(D) The synthesis of an important chiral alkaloid, 1-allyl-1,2,3,4-tetrahydro- β -carboline (**2**), from β -carboline (**1**) and a chiral auxiliary (R^*) was successfully achieved when TrocCl was employed to protect the N-2 position.⁸



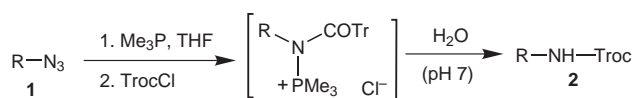
(E) Hydroxyalkylbenzimidazoles **1** with various alkyl chain lengths are selectively acylated with TrocCl in the preparation of benzimidazole functional acrylate monomers **2**.⁹



(F) TrocCl has recently been used in the synthesis of three novel C-2-C-3 unsaturated pyrrolo[2.1-c][1,4]benzodiazepine analogues containing conjugated acrylyl C-2 substituents.¹⁰ According to the authors, this reagent was chosen for its compatibility with both palladium coupling chemistry and pyrrolobenzodiazepine N-10-C-11 imine formation.



(G) Direct conversion of azide **1** to carbamate **2** in high yields (92%) can be achieved via a phosphazene route with TrocCl.¹²



References

- (1) Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, *14*, 1325.
- (2) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, **1999**, 281–282.
- (3) Ansari, A. M.; Craig, C. *Synthesis* **1995**, *2*, 147.
- (4) De Paulis, T.; Lovinger, D. M.; Martin, P. R. US Patent 2347879, **2003**.
- (5) Vesel, J.; Dzoganová, M.; Trnka, T.; Tislerová, I.; Saman, D.; Ledvina, M. *Synthesis* **2006**, *4*, 699.
- (6) Knight, D. W.; Leese, M. P. *Tetrahedron Lett.* **2001**, *42*, 2593.
- (7) Doi, T.; Numajori, Y.; Munakata, A.; Takahashi, T. *Org. Lett.* **2006**, *8*, 531.
- (8) Itoh, T.; Matsuya, Y.; Enomoto, Y.; Nagata, K.; Miyazaki, M.; Ohsawa, A. *Synlett* **1999**, *11*, 1799.
- (9) Woudenberg, R. C.; Coughlin, E. B. *Tetrahedron Lett.* **2005**, *46*, 6311.
- (10) Chen, Z.; Gregson, S. J.; Howard, P. W.; Thurston, D. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1547.
- (11) Huynh-Ba, T. US Patent 5395950, **1995**.
- (12) Sugiyana, S.; Watanabe, S.; Ishii, K. *Tetrahedron Lett.* **1999**, *40*, 7489.