SYNLETT Spotlight 199

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

2,2,2-Trichloroethyl Chloroformate (TrocCl)

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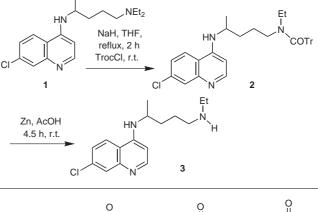
Introduction

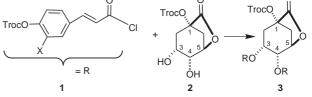
2,2,2-Trichloroethyl chloroformate (TrocCl, CCl₃CH₂OCOCl, bp 171–172 °C,) is a stable chloroformate which acylates aliphatic and aromatic hydroxyl and amino groups under mild conditions.^{1,2} This reagent is commercially available and has been widely used in regio-, chemo-, and stereoselective syntheses. The Troc group shows a sharp and charactereristic proton singlet at $\delta = 4.68-4.89$ 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 Aprotoxin A with protection and deprotection of an allyl ester intermediate with TrocCl was 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}





X = H (derivative of *p*-cumaric acid) or OMe (derivative of ferrulic acid)

SYNLETT 2007, No. 9, pp 1473–1474 Advanced online publication: 23.05.2007 DOI: 10.1055/s-2007-980374; Art ID: V20006ST © Georg Thieme Verlag Stuttgart · New York

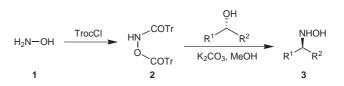
OH

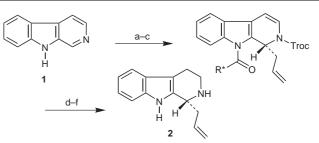
) _n

troc

(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





TrocCl

K₂CO₃, 0 °C

ΟН

H

NaOH, MeOH

1. Me₂P.

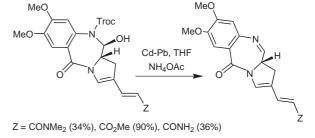
2. TrocCl

 $R - N_3$

1

(E) Hydroxyalkylbenzimidazoles 1 with various alkyl chain lengths are selectively acylated with TrocCl in the prepation 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.



2

H₂O

(pH 7)

NH-Troc

2

(G) Direct conversion of azide 1 to carbamate 2 in high yields (92%) can be achievied 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.

a: R*COCI; b: Bu₃CH₂CHCH₂; c: TrocCI; d: R* removal; e: Et₃SiH-TFA; f: Zn/AcOH