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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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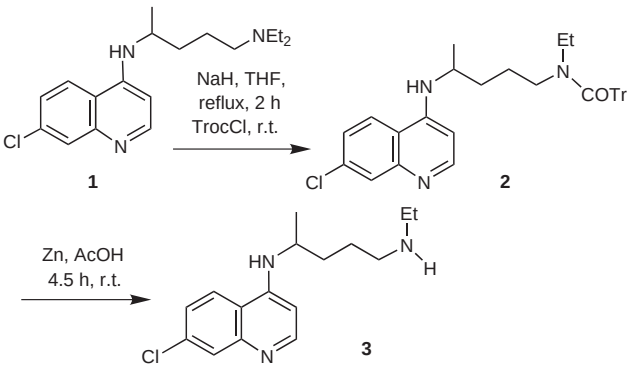
Introduction

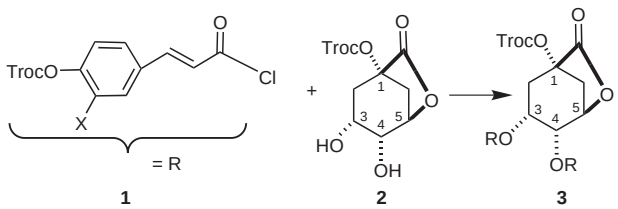
2,2,2-Trichloroethyl chloroformate (TrocCl, CCl_3CH_2OCOCl, bp 171–172 °C,) is a stable chloroformate which acylates aliphatic and aromatic hydroxyl and amino groups under mild conditions.[1,2] This reagent is commercially available and has been widely used in regio-, chemo-, and stereoselective syntheses. The Troc group shows a sharp and characterestic proton singlet at δ = 4.68–4.89 ppm, which makes its presence or absence easily detectable by ^{1}H 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.[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 Craig[3] 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)

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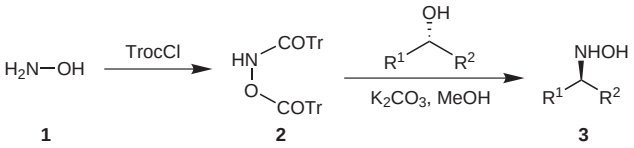
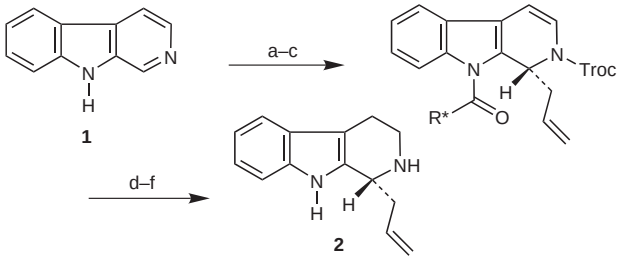
(C) Hydroxylamines **2** that are doubly N,O-protected with Troc are easily obtained from TrocCl and hydroxylamine (**1**). According to Knight and Leese,[6] these intermediates allow ready access to enantiopure hydroxylamines **3** starting from the corresponding secondary alcohols.

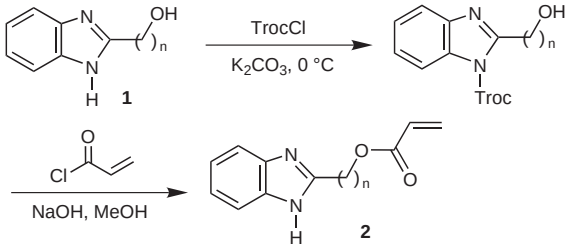


(D) The synthesis of an important chiral alkaloid, 1-allyl-1,2,3,4-tetrahydro-β-carboline (**2**), from β-carboline **1** and a chiral auxiliary (*R**) was successfully achieved when TrocCl was employed to protect the N-2 position.[8]

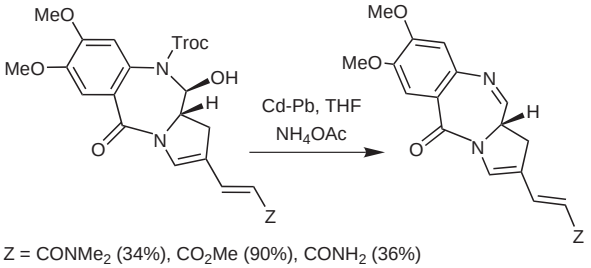


a: R*COCl; b: $Bu_3CH_2CHCH_2$; c: TrocCl;
d: R* removal; e: Et_3SiH-TFA; f: Zn/AcOH

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

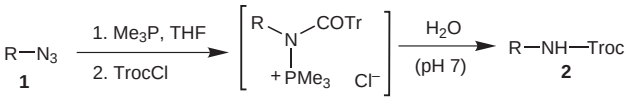


(F) TrocCl has recently been used in the synthesis of three novel C-2–C-3 unsaturated pyrrolo[2.1-*c*][1,4]benzodiazepine analogues containing conjugated acrylyl C-2 substituents.[10] According to the authors, this reagent was chosen for its compatibility with both palladium coupling chemistry and pyrrolobenzodiazepine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



Z = $CONMe_2$ (34%), CO_2Me (90%), $CONH_2$ (36%)

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



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