

TRICHLOROETHOXYCARBONYL: A GENERALLY APPLICABLE PROTECTING GROUP

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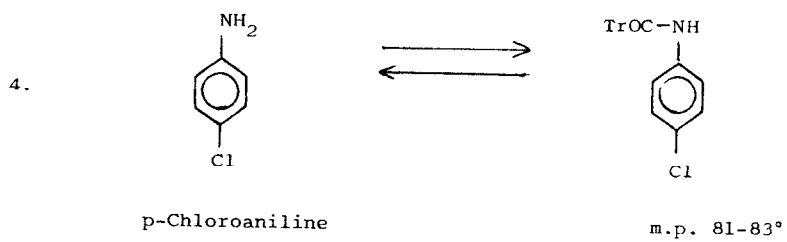
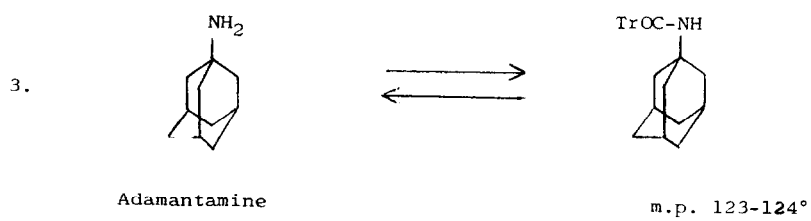
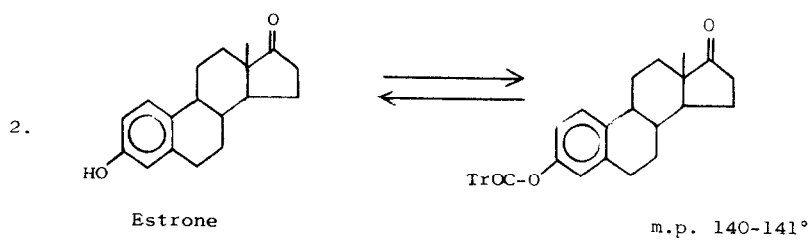
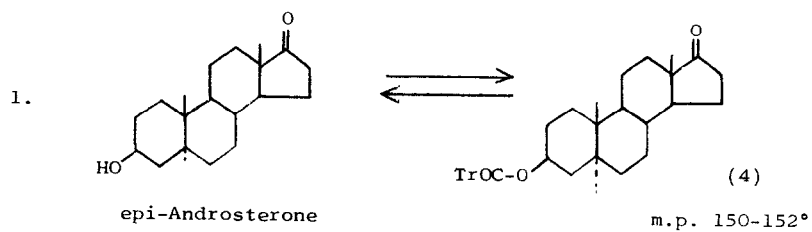
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Woodward and coworkers (1) have recently described the use of β,β,β -trichloroethyl as a carboxylic acid protecting group, while Grimshaw (2) has demonstrated the use of 2-iodoethoxycarbonyl as a protecting group in peptide synthesis. These masking groups could be removed by treatment with zinc dust in 90% acetic acid and zinc dust in methanol, respectively.

β,β,β -Trichloroethoxycarbonyl chloride, (3) [$\text{CCl}_3\text{CH}_2\text{OCOCl}$, b.p. 171-172°/760mm; 75-76°/60mm] a stable chloroformate, acylates aliphatic and aromatic hydroxyl and amino groups under mild conditions. The new carbonate esters and urethanes which we have prepared so far, could be easily purified by recrystallization.

The β,β,β -trichloroethoxycarbonyl group (for which we propose the designation TrOC-) also undergoes facile removal, affording the unmasked, original hydroxyl or amino functionalities by stirring 1-3 hrs. at room temperature with zinc dust in acetic acid or by brief reflux with zinc in methanol. Co-solvents, such as water, dioxane, etc. may also be used if needed. These conditions will leave a wide variety of other functional groups unaffected. Conversely, the new TrOC-derivatives are unaffected by conditions of the Sarett and Jones oxidations, room temperature exposure to dioxane-HCl overnight or trifluoroacetic acid for 30 minutes, and hydrogen at atmospheric pressure with palladium on charcoal in dioxane or platinum oxide in acetic acid.

To widen their utility in organic synthesis, the behavior of different TrOC-derivatives is being investigated under a variety of other conditions. The examples shown below, serve to illustrate some applications of the $\text{CCl}_3\text{CH}_2\text{OCO}$ -protecting group:



Acylation was carried out with excess $\text{CCl}_3\text{CH}_2\text{OCOCl}$ in pyridine and overnight stirring at room temperature, (5) or under Schotten-Baumann conditions. Reversal conditions are illustrated with the following typical experiment. A 107 mg. sample of the 3-TrOC-derivative of epiandrosterone was stirred with 107 mg. of Zn dust in 1.0 ml. of glacial acetic acid for 70 minutes. After filtration, the filtrate was diluted with water, extracted with chloroform and the recovered material recrystallized to give 56 mg. of epiandrosterone. (84% yield of reversal).

The unmasked products were characterized by m.p., I.R. and TLC. In the case of the amines, the filtrates were made strongly alkaline before extraction. Recovered amines were also characterized via their N-acetyl derivatives.

The $\text{CCl}_3\text{CH}_2\text{OCO}$ -group shows a sharp and characteristic two proton singlet at 5.25 τ (6) which makes its presence or absence easily detectable by NMR spectroscopy.

Acknowledgements

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References

1. R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ramgathan, H. Vorbruggen, J. Am. Chem. Soc. 88, 852 (1966).
R. B. Woodward, Science, 153, 487 (1966).
2. J. Grimshaw, J. Chem. Soc., 1965, 7136.
3. Germ. Pat. 358,125 (1922) and 491,492 (1930).
We have conveniently prepared the chloroformate by passing phosgene through a benzene, trichloroethanol, diethylaniline solution for 5 hours, acidifying, washing and drying the organic phase and distilling the product.
4. All new compounds were satisfactorily characterized by elemental analysis and spectral data.
5. Cf. Fieser's acylation conditions: L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero, T. Utne, J. Am. Chem. Soc., 74, 3309 (1952) and a recent comprehensive review on chloroformate chemistry: M. Matzner, R. P. Kurkijy and R. J. Cotter, Chem. Rev. 64, 645 (1964).
6. Determined on a Varian A-60 spectrometer in CDCl_3 using TMS as an internal reference.