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Selective removal of 2,2,2-trichloroethyl- and 2,2,2-trichloroethoxycarbonyl protecting groups with Zn–*N*-methylimidazole in the presence of reducible and acid-sensitive functionalities

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Abstract—Activated zinc dust in the presence of *N*-methylimidazole in ethyl acetate or acetone at reflux or room temperature removes 2,2,2-trichloroethyl- and 2,2,2-trichloroethoxycarbonyl protecting groups while azido-, nitro-, chloro-, phenacyl-, and *tert*-butyl ester functionalities as well as double bonds remain intact.

Removal of 2,2,2-trichloroethyl- (TCE) and 2,2,2-trichloroethoxycarbonyl (Troc) protecting groups is based on a reductive elimination process.[1] This feature makes this kind of protection orthogonal to several other protecting groups.[1b] Originally, TCE and Troc were removed by Zn in 90% aqueous AcOH,[2] but several modifications such as the use of Zn in MeOH, Zn in buffered THF–H_2O, Zn–Cu or Zn–Ag couples in MeOH, Zn–Pb in THF have been reported.[1] These procedures are carried out under protic (in some cases acidic) conditions. In one specific case, for the cleavage of bis-trichloroethyl-acetals, Zn was reported to be effective in EtOAc or THF without any additional reagent.[3] For eliciting the reductive elimination many other reagent systems have been applied: Li in liquid NH_3, SmI_2 in THF, Na–Hg in THF–MeOH, Cd in AcOH–DMF, Cd–Pb in AcOH, or electrolysis.[1] Some of these methods are performed under aprotic conditions, however, even those cannot be used with molecules having functional groups prone to reduction under the given circumstances.[4] Thus, the known deprotection conditions do not allow easily reducible or acid-sensitive groups to be retained in substrates.

In the course of a project to elaborate synthetic methodology to obtain anomeric α-amino acid derivatives, TCE ester **1**[5] (Table 1) needed to be deprotected. The classic Zn–AcOH conditions gave α-amino acid **2**[5] as expected. Applying Zn in EtOAc brought about no change. When Zn in the presence of *N*-methylimidazole[6] (NMI) in refluxing EtOAc was tried, an α-azido carboxylic acid derivative **3** was isolated as indicated by the 2130 and 3000–3500 cm^{-1} absorptions for the N_3 and the COOH groups, respectively, in the IR spectrum. This finding prompted us to test if these conditions could be applied with other substrates.

In trichloroethyl carbamate **4**[7] the azide was easier to reduce with Zn–AcOH than to remove the Troc protection as shown by the formation of glycosylamine **5**. The Zn–NMI system left the azide untouched and **6**[8] was formed accompanied by **7** which could be the result of an *O*/*N*-acetyl migration.

Further experiments were carried out with aromatic model compounds. The nitro group of TCE ester **8** and Troc derivatives **11** and **14** was reduced with Zn–AcOH to give **9**, **12**, and **15**, respectively, but survived with Zn–NMI as indicated by the deprotected products **10**, **13**, and **16**, respectively. Neither conditions removed the aromatic chloride of **17** as shown by the formation of **18** in both reactions.

The double bond in **19** was partially reduced by zinc in 90% acetic acid to give a mixture of **20** and **21**. On the other hand removal of the TCE ester gave only **21** both under Zn–glacial acetic acid and Zn–NMI conditions.

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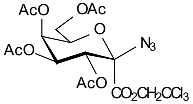
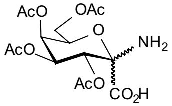
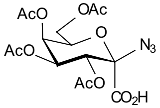
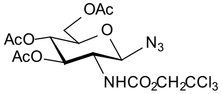
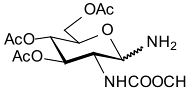
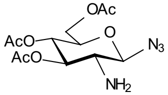
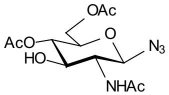
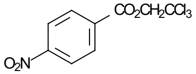
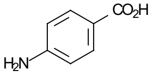
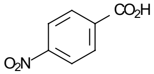
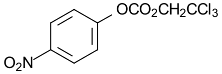
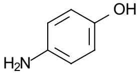
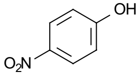
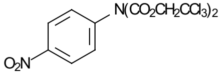
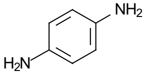
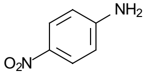
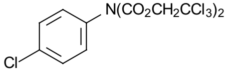
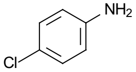
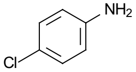
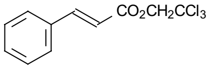
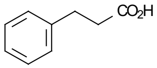
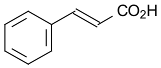
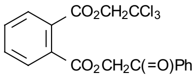
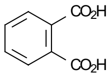
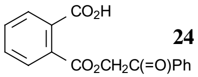
Table 1. Removal of 2,2,2-trichloroethyl- or 2,2,2-trichloroethoxycarbonyl groups with zinc[a]

Starting material		Products (yield) under the specified reaction conditions		
		A: Zn, 90% aq AcOH, 0 °C ***B***: Zn, glacial AcOH, rt	***C***[b]: Zn–*N*-methylimidazole (NMI)	Solvent, temp, eq NMI, reaction time
	**1**	 **2** ***B***: 2 h (45%)	 **3** (59%)	EtOAc, reflux, 3 NMI, 8 h
	**4**	 **5** ***B***: 2 h (68%)	 **6** (43%) +  **7** (25%)	EtOAc, reflux, 3 NMI, 6 h
	**8**	 **9** ***A***: 1 h (49%) ***B***: 2 h (66%)	 **10** (61%)	Acetone, rt, 3 NMI, 5 d
	**11**	 **12** ***A***: 18 h (63%) ***B***: 2 h (45% **12** + **13** 5:1)	 **13** (59%)	EtOAc, reflux, 3 NMI, 3.5 h
	**14**	 **15** ***A***: 0.5 h (95%)	 **16** (80%)	EtOAc, reflux, 1 NMI, 20 h
	**17**	 **18** ***B***: 0.5 h (81%)	 **18** (60%)	EtOAc, reflux, 3 NMI, 1 h
	**19**	 ***A***: 24 h (65% **20** + **21** 1:10) ***B***: 1 h (80% **21**)	 **21** (62%)	Acetone, reflux, 3 NMI, 5 h
	**22**	 **23** ***A***: 5 h (83%)	 **24** (54%)	EtOAc, rt, 3 NMI, 27 h
$Cl_3CCH_2OCONHCH_2CO_2$*t*-Bu **25**			$H_2NCH_2CO_2$*t*-Bu **26** (57%)	EtOAc, reflux, 3 NMI, 6 h

[a] Without any additive, activated Zn in EtOAc at reflux temperature caused no change in the starting materials.

[b] *Typical reaction conditions*: the starting material (0.5 mmol) was dissolved in dry solvent (3–5 ml), Zn dust (5 mmol, activated by washing with 2 M HCl, water, acetone, ether, then dried) and NMI were added and the mixture was vigorously stirred (for solvent, NMI equivalents, reaction temperature and time see Table 1). Workup: filtration through Celite, (in the case of products of acidic character, acidification by dilute HCl), washing with water, drying, evaporation of the solvent, followed by crystallization or column chromatography. Products **3** and **5**–**7** were characterized by IR, ^1H and ^{13}C NMR spectra (see electronic supplementary information). Products from reactions with model compounds were identified by comparing their ^1H NMR spectra with those of authentic samples.

Phenacyl groups are used for the protection of carboxylic acids and phenols, and their removal can also be effected by Zn–AcOH.[1] Trichloroethyl-phenacyl phthalate **22** was cleaved to phthalic acid **23** by zinc in 90% aq. AcOH as expected. The use of the Zn–NMI system, however, left the phenacyl moiety intact and removed the TCE protection only resulting in **24**.

Troc-*N*-Gly-O*t*-Bu **25** was also deprotected by Zn–NMI to give glycine *tert*-butyl ester **26** demonstrating the survival of an acid sensitive group under the new conditions.

In summary, Zn–*N*-methylimidazole in an aprotic solvent represents a new reagent system for the selective removal of TCE and Troc protecting groups in the presence of azido-, nitro-, chloro-, phenacyl-, and *tert*-butyl ester functionalities as well as double bonds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.026.

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