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New deprotection method of the 2,2,2-trichloroethoxycarbonyl (Troc) group with $(Bu_3Sn)_2$

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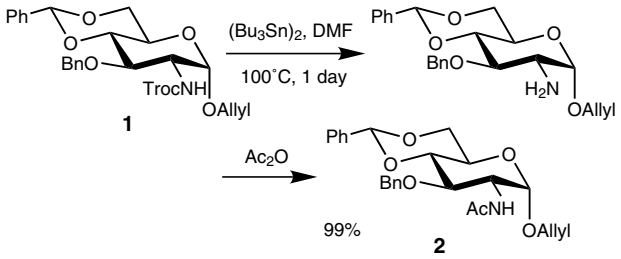
Abstract—The 2,2,2-trichloroethoxycarbonyl (Troc) group was efficiently removed in high yields with $(Bu_3Sn)_2$ in DMF under microwave heating. The present method was applied to deprotection of the Troc group on solid support.

The 2,2,2-trichloroethoxycarbonyl (Troc) group has been frequently used for the protection of amino and hydroxyl groups in organic synthesis, especially oligosaccharide synthesis.[1] For example, β-selective glycosylation of the glucosaminyl donor is readily effected by virtue of neighboring participation of the 2-*N*-Troc group.[2] The Troc group is generally removed via a reductive elimination process, such as Zn in AcOH, Zn–Cu in AcOH, Zn–Pb in THF, Zn–*N*-methylimidazole,[3] Li in liquid NH_3, SmI_2 in THF, Cd in AcOH–DMF, or electrolysis.[1] Most of these methods are carried out under heterogeneous conditions and hence are difficult to apply to solid-phase synthesis. In addition, we have sometimes observed that significant amounts of dichloroethoxycarbonylated byproducts were formed by the cleavage of the Troc group with Zn or Zn–Cu in AcOH.

We assumed that the Troc group would be removed via a radical intermediate formed by abstraction of the chlorine atom and, therefore, expected that the radical generating reagents could cleave the Troc group. We first examined the reaction by using *N*-Troc-glucosamine allyl glycoside **1** and AIBN (0.1 equiv) and Bu_3SnH (1.1 equiv), Et_3B (1.1 equiv), or $(Bu_3Sn)_2$ in benzene or toluene under reflux, but the cleavage of the Troc group proceeded very slowly to give only a tiny amount of the desired product. We then checked the cleavage reaction of the Troc group in DMF considering the application of the present method to solid-phase synthesis. Previously, we reported solid-phase synthesis of indol-2-ones (2-oxindoles) by means of aryl radical cyclization of resin-bound *N*-(2-bromophenyl)acrylamides using Bu_3SnH.[4] We found that DMF was the best choice for the radical cyclization on solid support inducing a reagent concentration effect of Bu_3SnH on the polymer support, whereas the same reaction in DMF under liquid-phase condition did not proceed. Surprisingly, the Troc group was removed quantitatively by using $(Bu_3Sn)_2$ (0.6 equiv) in DMF without any effect on the allyl group. The resulting amino group was then acetylated for easy purification to give the desired **2** in 99% yield. AIBN and Bu_3SnH in DMF gave many byproducts, including dichloroethoxycarbonylated compounds (yield of **2** was 17%). Et_3B also cleaved the Troc group but afforded the ethyl group adduct to the allyl group.



We next examined the removal of the Troc group with $(Bu_3Sn)_2$ under microwave irradiation to reduce the reaction time. Deprotection in benzene hardly proceeded even under microwave irradiation (Table 1, entry 1). Microwave irradiation dramatically accelerated

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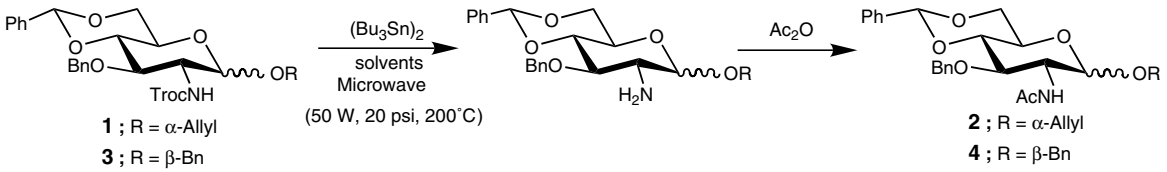
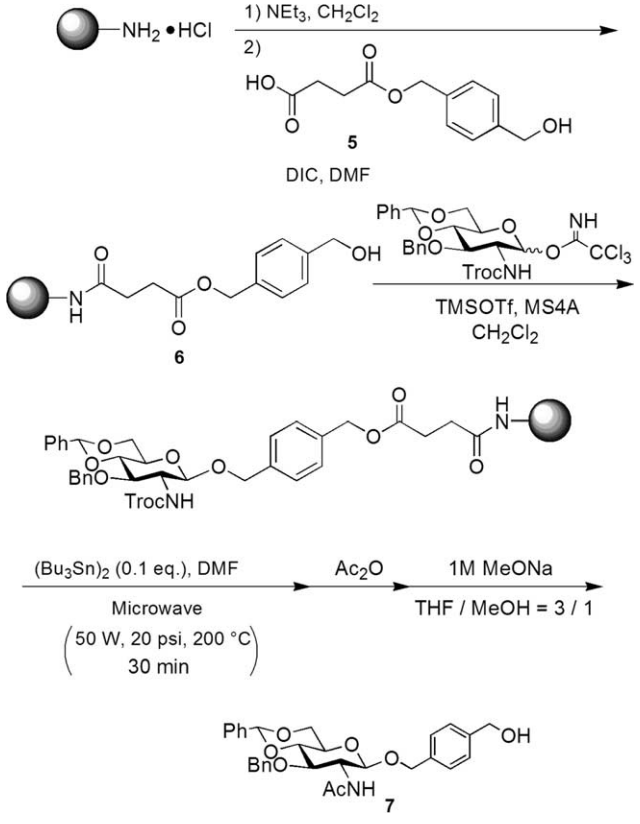
Table 1. Deprotection of Troc group under microwave irradiation



Entry	Solvent	Substrate	$(Bu_3Sn)_2$ (equiv)	Time (min)	Product	Yield (%)
1	Benzene	**1**	0.6	500	**2**	Trace
2	DMF	**1**	0.6	50	**2**	89
3	DMF	**3**	0.6	40	**4**	94
4	DMF	**1**	0.1	50	**2**	82
5	DMF	**3**	0.1	40	**4**	99

deprotection of the Troc group in DMF (entries 2 and 3).[5,6]

Interestingly, a catalytic amount of $(Bu_3Sn)_2$ was enough to complete the deprotection reaction (Table 1, entries 4 and 5). Probably, Bu_3SnCl formed by the reaction was reacted with the tributylstannyl radical to regenerate $(Bu_3Sn)_2$ and form a chlorine radical, which might be reduced by DMF. Addition of excess radical trapping agent anthracene prevented the cleavage reaction of the Troc group. This result proved that the present cleavage of the Troc group is radical-promoted reaction.



We then applied the present method to solid-phase synthesis, since the cleavage reaction is carried out under homogeneous conditions. The reaction sequence began with the introduction of linker **5** to aminomethylated polystyrene by amide bond formation. *N*-Troc glucosamine was then introduced to solid support by the trichloroacetimidate method.[7] Deprotection of the Troc group on solid phase was carried out by the use of $(Bu_3Sn)_2$ (0.1 equiv) in DMF under microwave irradiation. The resulting resin was acetylated and cleaved by NaOMe in THF/MeOH to give the desired **7** in 88% for five steps.

As described, we have established a new deprotection method of the Troc group by using $(Bu_3Sn)_2$ in DMF. The present method did not afford dichloroethoxycarbonylated byproducts.

Acknowledgements

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5. Discover™ Focused Microwave Synthesis (CEM Corporation) was used for focused microwave irradiations. A vessel for microwave reaction was filled with **1**, DMF and $(Bu_3Sn)_2$, and then sealed with a Teflon septum. The vial was positioned in the cavity of the microwave reactor and irradiated with maximum power of 50 W for 50 min. After cooling, Ac_2O was added. The mixture was concentrated in vacuo and the residue was washed with *n*-hexane to give **2**.
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