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A Novel Protecting Group for Hindered Phenols

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Abstract: Boc_2O and DMAP were used to protect hindered phenols as their Boc derivatives under mild conditions. Deprotection conditions were developed to suppress loss of a *tert*-butyl group from the aromatic ring, or alkylation of an additional *tert*-butyl group at an unsubstituted *ortho* or *para* position.

A variety of protecting groups have been used for protection of phenols,[2] but few of these have been applied to hindered phenols such as di-*tert*-butyl phenols. Due to steric congestion, introduction and particularly removal of protecting groups on hindered phenols requires harsh conditions.[3] A removable protecting group was required for the substrate shown in entry 5 of the Table which would allow for subsequent metal-halogen exchange using *n*-butyllithium. The *tert*-butoxycarbonyl (Boc) group was considered since hindered carboxamides are readily protected using di-*tert*-butyldicarbonate (Boc_2O) and 4-dimethylaminopyridine (DMAP) if they are sufficiently acidic.[4] We now show that the high acidity of phenols allows for the facile introduction of a Boc protecting group even for hindered phenols.[5] Conditions for removal of the Boc group have been discovered that avoid side reactions resulting from the liberated *tert*-butyl cation or from de-alkylation of the desired di-*tert*-butyl phenol products.

Results for the protection and deprotection of a series of phenols is provided in the Table. All substrates were commercially available except the entry 4 substrate.[6] Although CH_3CN or CH_2Cl_2 have been routinely used as solvents during the Boc protection of carboxamides, hexanes was found to give a cleaner product in entry 7, and this solvent was subsequently employed for all substrates. The moderately hindered phenols in entries 1-3 reacted rapidly and only a slight excess of Boc_2O was required for complete conversion. The di-*tert*-butylphenols reacted slowly and 1.2 equiv of Boc_2O was necessary for complete conversion due to competition of the liberated *tert*-butyl alcohol for Boc_2O. Isolated product yields were high and in some cases no purification was required.

Our initial attempt to deprotect the *O,N*-bis-Boc protected derivative in entry 4 was surprising. Both Boc groups were readily removed using neat trifluoroacetic acid (TFA, 60 equiv) over 1 h; however, a by-product where one of the *tert*-butyl groups from the aromatic ring was lost was isolated in 10% yield. This Friedel-Crafts-like de-alkylation[7] could be suppressed by using 10 equiv of TFA in CH_2Cl_2 and carefully monitoring the reaction for completion. Under the standard conditions A in the Table, the Boc protected phenols in entries 5 and 8 were cleanly deprotected, while the phenol in entry 7 gave 4% de-alkylation. The "basicity" of the aromatic ring makes it susceptible to acid promoted de-alkylation only for the trialkyl substituted phenols.

Application of the standard TFA deprotection conditions A to substrates with unsubstituted *ortho* or *para* positions afforded a by-product where the liberated *tert*-butyl cation alkylated the aromatic ring. This alkylation product amounted to 43% of the deprotected crude product in entry 1, 5% in entry 2, 10% in entry 3 and 21% in entry 6. This side reaction was anticipated since phenol or anisole are frequently used as *tert*-butyl cation scavengers during cleavage of Boc groups.[8] It was hoped that this side reaction could be avoided by providing an alternate scavenger. Conditions B in the Table were developed wherein water presumably traps the *tert*-butyl cation in preference to the phenol.[9] These conditions afforded high yields of the corresponding phenols without any detectable alkylation products for entries 2, 3 and 6 and with only 2% of the alkylation product for entry 1.

In summary, we have developed mild conditions to protect hindered phenols as their Boc derivatives. Two potential side reactions were identified during deprotection studies: loss of a *tert*-butyl group from the phenol ring and alkylation of an additional *tert*-butyl group at an unsubstituted *ortho* or *para* position. Both side reactions were suppressed by suitable choice of reaction conditions and high yields of phenols were realized.

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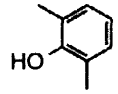
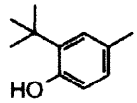
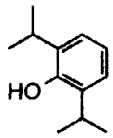
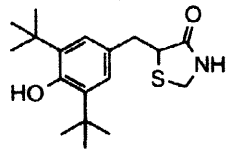
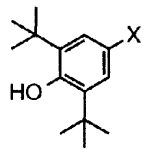
Table. *tert*-Butoxycarbonyl Protection and Deprotection of Hindered Phenols

		Protection			Deprotection	
Entry	Substrate	Rxn time	Yield (%)	Conditions	Rxn time (h)	Yield (%)
1		5 min	98	B	3	91
2		20 min	100	B	3	85
3		30 min	95	B	3	87
4		3 h	89	A	5	94
						
5	X = Br	6 h	94	A	19	89
6	X = H	19 h	93	B	3	89
7	X = CH_3	28 h	100	A	21	79
8	X = OCH_3	41 h	83	A	28	100

Representative Procedures

Protection: The phenol substrate and Boc_2O (1.02 equiv entries 1-3, 2.2 equiv entry 4, 1.2 equiv entries 5-8) were dissolved in hexanes (0.7 M, entry 4 substrate dissolves only after an initial rapid Boc protection of the amide nitrogen[4]) and DMAP (0.05 equiv) was added. When the reaction was complete as judged by TLC, the mixture was partitioned between ethyl acetate, brine and 1 N HCl. The layers were separated and the organic layer was washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated. The products in Entries 1, 2, 5, 6 and 8 were purified by chromatography on flash silica gel. All of the Boc derivatives except for entry 6[5] were new compounds and had satisfactory spectral and microanalytical data.

Deprotection Conditions A: The substrate was dissolved in CH_2Cl_2 (0.5 M) and treated with 3 equiv of TFA. When the reaction was complete as judged by TLC or HPLC, the mixture was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and evaporated.

Deprotection Conditions B: The substrate was dissolved in dioxane (10 mL per g substrate) and an equivalent volume of 3 M HCl was added. The mixture was heated at reflux for 3 h, then partitioned between EtOAc and aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and evaporated.

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[1] A Lilly Research Laboratories Summer Internship for J. R. R. is gratefully acknowledged.

[2] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd Ed., Wiley: New York, 1991, pp. 145-174.

[3] Trimethylsilyl: Friedman, S.; Kaufman, M. L.; Wender, I. *J. Org. Chem.* **1962**, *27*, 664-666. MOM: Introduced under mild conditions but could not be removed under acidic conditions without decomposition of phenol. Hansen, M.M., unpublished results.

[4] Hansen, M. M.; Harkness, A. R.; Coffey, D. S.; Bordwell, F. G.; Zhao, Y. *Tetrahedron Lett.* **1995**, *36*, 8949-8952.

[5] Strongly basic phase transfer conditions with Boc_2O have been used to convert di-*tert*-butylphenol to the Boc protected derivative in 7% yield, see: Houlihan, F.; Bouchard, F.; Frechet, J. M. J.; Willson, C. G. *Can. J. Chem.* **1985**, *63*, 153-162.

[6] Prepared as described, see: Hansen, M. M.; Harkness, A. R. *Tetrahedron Lett.* **1994**, *38*, 6971-6974.

[7] For de-alkylation of di-*tert*-butylphenols using $AlCl_3$, see: Tashiro, M.; Fukata, G. *J. Org. Chem.* **1977**, *42*, 1208.

[8] See ref 2 pp. 327-329.

[9] Aqueous H_2SO_4 in dioxane eliminated *tert*-butylation of tryptophan during peptide Boc cleavage, see: Houghten, R. A.; Beckman, A.; Ostresh, J. M. *Int. J. Peptide Protein Res.* **1986**, *27*, 653-658.