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Reductive Cleavage of Aryl *O*-Carbamates to Phenols by the Schwartz Reagent. Expedient Link to the Directed *Ortho* Metalation Strategy‡

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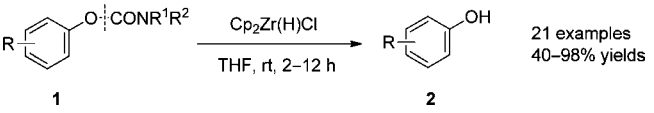
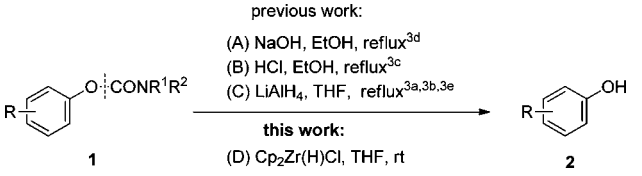
ABSTRACT



A general, mild, and efficient method for the reductive cleavage of aryl *O*-carbamates to phenols, 1 → 2 using the Schwartz reagent is reported. The method is selective, tolerating a large number of functional groups; may be carried out by direct or by an economical *in situ* procedure; and, notably, establishes a synthetic connection to the directed *ortho* metalation strategy (Figure 1) allowing new entries into difficult to prepare contiguously substituted aromatics and heteroaromatics.

Recently, we developed[1] the use of an *in situ* Schwartz reagent for the general and efficient conversion of aryl amides to benzaldehydes which, especially in conjunction with the appreciated directed *ortho* metalation (DoM) chemistry of benzamides,[2] provides a new and general synthetic strategy for the construction and manipulation of polysubstituted aromatic and heteroaromatic aldehydes. In the quest for further applications, we turned to the aryl *O*-carbamates ($ArOCONR_2$), the most powerful directed metalation group (DMG),[2] whose recalcitrance to mild hydrolytic or reductive cleavage[2b,d,3] to phenols has denied its broader use. Based on the structural similarity to amides and the IR and NMR evidence of Zr-coordination to a variety of unsaturated groups,[4] we rationalized that the tertiary *O*-carbamate may be susceptible to reduction by the Schwartz reagent. Herein we report on the ArO-$CONR_2$ to ArOH conversion, **1** → **2** (Scheme 1, D), which occurs under mild conditions and is as highly selective as for the corresponding amide,[1] tolerating a host of standard functional groups. Significantly, we show that, linked with the DoM strategy, the Schwartz reduction method furnishes difficult to prepare, contiguously substituted phenols of anticipated value in organic synthesis.

Scheme 1. Methods for Cleavage of Aryl *O*-Carbamates to Phenols



In initial studies,[5] we used the Georg amide reduction procedure[6] for the Schwartz reagent mediated aryl *O*-carbamate to phenol conversion.

‡ Dedicated to Prof. Carmen Najera on the occasion of her 60th birthday.

(1) Zhao, Y.; Snieckus, V. Submitted.

(2) (a) Snieckus, V.; Macklin, T. In *Handbook of C−H Transformations*; Dyker, G., Ed.; Wiley: Weinheim, 2005; Vol. 1, p 106. (b) Clayden, J. In *Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2004; Vol. 1, p 495. (c) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley: Weinheim, 2002; p 330. (d) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(3) (a) Schoen, U.; Messinger, J.; Solodenko, W.; Kirschning, A. *Synthesis* **2012**, *44*, 3822. (b) Yamazaki, K.; Kawamorita, S.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 3978. (c) Hao, X.-Y.; Zhou, Z.-M.; Xue, W.-Z.; Yin, J.; Xu, B.-C. *Youji Huaxue* **2008**, *28*, 1756. (d) Sanz, R.; Castroviejo, M. P.; Fernandez, Y.; Fananas, F. J. *J. Org. Chem.* **2005**, *70*, 6548. (e) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935.

(4) Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1971**, *27*, 373.

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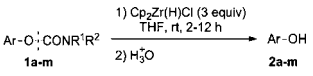
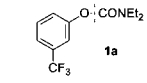
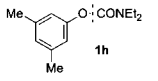
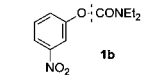
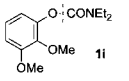
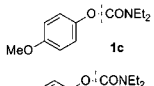
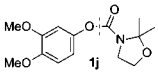
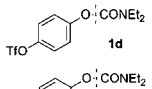
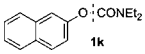
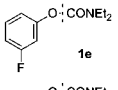
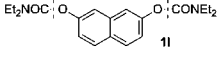
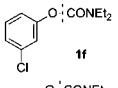
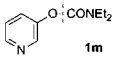
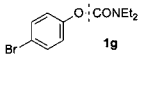
In the first trial study, *N*,*N*-diethyl naphthalene 2-*O*-carbamate (chosen because of nonvolatility of the expected product) with freshly prepared[5,7] Schwartz reagent (3 equiv) in THF at rt for 3 h led to complete conversion of starting material and afforded 2-naphthol in 97% yield (Table 1, entry 11). Application of these conditions to a variety of aryl *O*-carbamates derived from commercially available phenols afforded the corresponding phenols in moderate to excellent yields. Selected were a variety of *ortho*-, *meta*-, and *para*-substituted derivatives with both electron-donating groups (EDGs) and electron-withdrawing groups (EWGs). Tolerance of *ortho*-substituted derivatives was observed (entry 9). In the *meta*-series, useful results were achieved for the nitro (entry 2) and the dimethyl (entry 8) *O*-carbamates and, more significantly, for the trifluoromethyl, fluoro, and chloro systems (entries 1, 5, and 6) all of which are potential candidates for synergistic in-between DoM[2a,d] creating opportunities for synthesis of difficult to prepare 1,2,3-substituted phenols. In the *para*-series, aside from the *para*-OMe system (entry 3), equally significant synthetic opportunity is presented by the *para*-OTf and *para*-bromo derivatives (entries 4 and 7) on which Suzuki and related cross-coupling may be achieved before or after the Schwartz reagent cleavage of the *O*-carbamates and thereby lead to substituted hydroxy biaryls. Potential DoM links are also available for the naphthalene 2-*O*-carbamate (entry 11), the bis-*O*-carbamate (entry 12) which, unsurprisingly, required 6 equiv of Schwartz reagent, and the pyridine 3-*O*-carbamate (entry 13) all of which afforded phenolic products in very good yields. For further scope extension, the reduction of an oxazolidine *O*-carbamate was also achieved in high yield (entry 10).

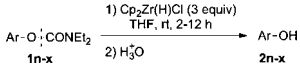
Table 1. Schwartz Reagent Mediated Reduction of Aryl *O*-Carbamates Using the Georg Procedure

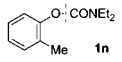
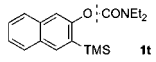
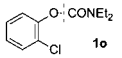
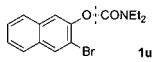
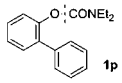
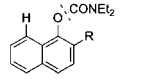
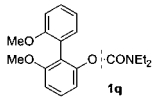
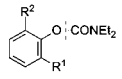
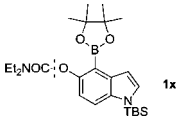


entry	substrate	yield (%)[a]	entry	substrate	yield (%)[a]
1	 **1a**	91	8	 **1h**	92
2	 **1b**	91[b]	9	 **1i**	78
3	 **1c**	98	10	 **1j**	90
4	 **1d**	80	11	 **1k**	97
5	 **1e**	95	12	 **1l**	82[c]
6	 **1f**	88	13	 **1m**	87
7	 **1g**	88			

[a] Yields of isolated products. [b] 5 equiv of Schwartz reagent required for full conversion. [c] 6 equiv of Schwartz reagent required.

Table 2. Schwartz Reagent Mediated Reduction of DoM-Derived Aryl *O*-Carbamates Using the Georg Procedure



entry	substrate	yield (%)[a]	entry	substrate	yield (%)[a]
1	 **1n**	82	7	 **1t**	55
2	 **1o**	89[b]	8	 **1u**	87
3	 **1p**	88			
4	 **1q**	88	9	R = I (**1v**)	0
			10	= TES(**1w**)	0
5	$R^1 = R^2$ = Me (**1r**)	0	11	 **1x**	40
6	R^1 = OMe; R^2 = TMS (**1s**)	0			

[a] Yields of isolated products. [b] Due to the high volatility of 2-chlorophenol, it was benzylated for ease of isolation.

Although, as noted in the discussion for Table 1, a number of *O*-carbamates may be derived by or are suitable for DoM and cross-coupling related chemistry, direct demonstration of such a synthetic link was sought and established (Table 2). Thus, Schwartz reduction of two DoM-derived *ortho*-substituted phenyl *O*-carbamates (entries 1 and 2) proceeds very well and biaryl *O*-carbamates (entries 3 and 4), derived by DoM–Suzuki–Miyaura cross-coupling regimens,[8] undergo Schwartz reagent cleavage to phenols in high yields. 3-TMS and 3-halo substituted naphthalene 2-*O*-carbamates likewise are smoothly converted to the corresponding phenols (entries 7 and 8). The newly developed regioselective DoM preparation of

(5) Morin, J. M.Sc. Thesis, Queen's University, Kingston, ON, Canada, 2007.

(6) (a) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408. (b) White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 11995.

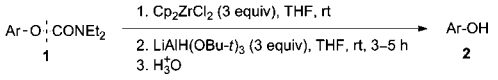
(7) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1993**, *71*, 77.

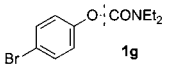
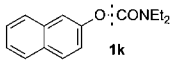
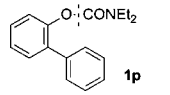
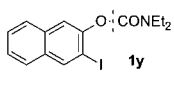
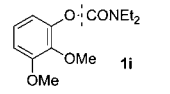
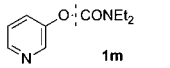
(8) (a) See Supporting Information. (b) Anctil, E. J. G.; Snieckus, V. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley: Weinheim, 2004; Vol. 2, p 761. (c) Anctil, E. J. G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150.

(9) (a) Groom, K.; Nilewski, C.; Morin, J.; Snieckus, V. In preparation. (b) 3-Br-2-naphthalene *O*-carbamate is also available by *ipso*-bromodesilylation of the corresponding TMS derivative; see ref 5.

(10) Electrophilic bromination affords either 1-bromo or 1,6-dibromo 2-naphthols; see: Koelsch, C. F. *Org. Synth.* **1955**, *20*, 18.

Table 3. Reductive Cleavage of Aryl *O*-Carbamates to Phenols via the *in situ* Schwartz Method



entry	substrate	yield (%)[a,b]	entry	substrate	yield (%)[a,b]
1	 **1g**	96 (88)	4	 **1k**	95 (97)
2	 **1p**	89 (88)	5	 **1y**	81
3	 **1i**	90 (78)	6	 **1m**	90 (87)

[a] Yields of isolated products. [b] Yields in parentheses refer to direct Schwartz reduction; see Table 1.

these derivatives[5,9] allows access to simple 3-substituted-2-naphthols which are expensive and/or not easily available.[10] The Schwartz reagent cleavage of the indole 4-boropinacolato 5-*O*-carbamate to the corresponding phenol (entry 11), albeit in low conversion, demonstrates the potential stability of boronates to the reduction conditions. The sensitivity to steric effects is demonstrated by the failure to effect reduction of the 2,6-disubstituted phenyl *O*-carbamates (entries 5 and 6) and the naphthyl *O*-carbamates (entries 9 and 10).

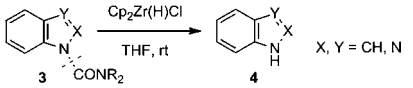
Our recent discovery of the economically and practically advantageous *in situ* Schwartz conditions for the amide to aldehyde transformation[1] logically led to its application to the $ArOCONR_2 \rightarrow ArOH$ transformation. Table 3 establishes that the *in situ* method is very effective for this reduction, being complete in several hours (TLC analysis) to give good yields of isolated phenol products.[11] Thus, overall, in comparison with the direct Schwartz reagent reduction, the *in situ* method is a practical, equally efficient, and much less expensive process for the reductive cleavage of aromatic *O*-carbamates to phenols[12] which, by these preliminary studies, appears to tolerate all functional groups previously established for the Georg amide reduction method.[6]

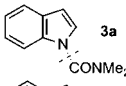
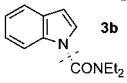
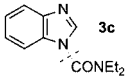
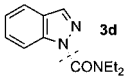
As a further brief extension, reductive cleavage of heterocyclic *N*-amides by the Schwartz reagent was tested. Thus, treatment of the indole- and benzimidazole-*N*-amides **3a**–**3c** with the Schwartz reagent (2 equiv) led successfully to carbamoyl reductive cleavage in good yields (Table 4, entries 1–3). In the indazole case, **3d**, a 56% yield of the expected product **4da** was obtained accompanied by the over-reduction side product **4db** (43% yield) which

(11) In terms of visual observation, unlike *in situ* amide reduction (no precipitate formed), the *O*-carbamate reduction showed the appearance of precipitation which is assumed to be the Schwartz reagent that slowly is solubilized by the reaction forming the tetrahedral intermediate as surmised by Georg in the amide reduction mechanism postulate; see ref 6a.

(12) Zhao, Y. Ph.D. Thesis, Queen's Univesity, Kingston, ON, Canada, 2010.

Table 4. Reductive Cleavage of Heterocyclic *N*-Amides Using the Schwartz Reagent



entry	substrate	equivalent of Schwartz reagent	time	product	yield (%)[a]
1	 **3a**	2.0	40 min	 **4a**	88
2	 **3b**	2.0	1 h	 **4a**	94
3	 **3c**	2.0	15 min	 **4c**[b]	82
4	 **3d**	3.0[c]	30 min	 **4da**	56
				 **4db**[d]	43

[a] Yields of isolated products. [b] Boc protection to facilitate product isolation. [c] 3 equiv required for complete conversion. [d] **4db** can be converted into **4da**; see ref 13.

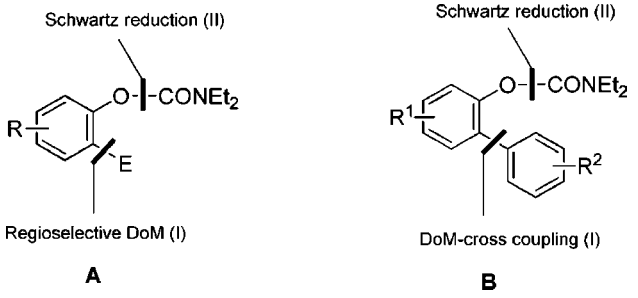


Figure 1. Synthetic potential of combined *O*-carbamate DoM–Schwartz reduction chemistry.

may be fully converted into **4da** under acidic conditions (entry 4).[13] Since *N*-$CONEt_2$ indole is an excellent DMG for the synthesis of 2- and/or 7-substituted indoles,[14] this method may be used to advantage on indole derivatives for DMG removal after DoM reactions.

In conclusion, a general, mild, and efficient method for the reductive cleavage of aryl and heteroaryl *O*-carbamates to the corresponding phenols using the Schwartz reagent has been demonstrated.[15] As for the benzamide to benzaldehyde conversion,[1] both direct (Georg) and the new,

(13) Atkinson, F. L.; Barker, M. D.; Campos, S. A.; Harrison, L. A.; Parr, N. J.; Patel, V. K. Patent Application: WO 2007028445, 2007.

(14) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899.

(15) As already partially implied in ref 1, the OSO_2NEt_2 and $OP(O)(NEt_2)_2$ groups are inert to reduction; see also ref 12.

more economical, *in situ O*-carbamate reduction methods constitute useful procedures for the synthesis of a range of phenols which are expensive, are unavailable, or require elaborate preparative methods. Thus, the following useful synthetic opportunities may be anticipated: combined DoM−Schwartz reduction and DoM−Suzuki cross-coupling−Schwartz reduction protocols for the construction of difficult to access contiguous 1,2- and 1,2,3-substituted and other multisubstituted phenols (Figure 1, A and B). Finally, in view of the establishment of a selective amide to aldehyde over *O*-carbamate to phenol reduction priority and the highest ranking of the $OCONEt_2$ DMG, manipulation of such systems (Figure 1, A when R = $CONEt_2$) by DoM chemistry prior to Schwartz reduction offers additional wide-ranging synthetic value.[16]

(16) For detailed results of both Schwartz reduction procedures, see ref 12, ref 5, and full paper in preparation.

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Supporting Information Available. Experimental procedures and analytical data for new compounds and products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.