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## Novel, base-promoted reaction of N-alkoxycarbonyl-O-(halosubstituted 4-nitrophenyl)hydroxylamines

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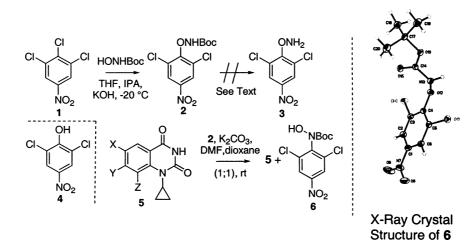
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**Abstract**—This paper describes base-promoted reactions of *N*-alkoxycarbonyl-*O*-(nitrophenyl)hydroxylamines which contain a halogen attached to the aromatic ring. The reaction is promoted under mild conditions (NaHCO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub>) and provides the *N*-alkoxycarbonyl-*N*-hydroxyaniline. In a crossover experiment, some scrambling was observed which suggests that the reaction is inter- and intramolecular in nature. *N*-Boc-(2,6-di-Cl-4-NO<sub>2</sub>-phenyl)hydroxylamine was also found to *N*-Boc aminate Bn<sub>2</sub>NH to form the protected hydrazine in modest yield. © 2002 Elsevier Science Ltd. All rights reserved.

During the course of the preparation of various O-(4nitrophenyl)hydroxylamines as electrophilic aminating agents, we attempted to prepare O-(2,6-dichloro-4nitrophenyl)hydroxylamine **3** by Boc cleavage of **2** (Scheme 1). We were not able to prepare this material by normal means,<sup>1</sup> and only isolated phenol **4**. An attempt was made to aminate imide **5** by reaction with N-Boc **2** under our standard aminating conditions.<sup>2</sup> We were quite surprised to find that under the standard conditions which we used for amination, N-Boc phenylhydroxylamine **2** had been transformed into N-Boc-N- hydroxyaniline **6** (unambiguously established by single-crystal X-ray analysis;<sup>3</sup> Scheme 1). After structural identification, we wondered if this reaction was somewhat general and mechanistically if the reaction was inter- or intramolecular in nature. This manuscript describes these investigations as well as attempts to directly use **2** as an electrophilic, protected nitrogen source.

The base-promoted reaction of *N*-Boc-(halosubstituted-4-nitrophenyl)hydroxylamines<sup>1</sup> was explored using 1.5



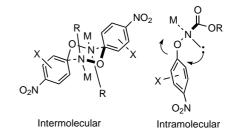
Scheme 1.

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equiv. of  $K_2CO_3$ , NaHCO<sub>3</sub>, or KHCO<sub>3</sub> in a 1:1 mixture of DMF and dioxane at either 22 or 55°C. These conditions proved sufficient to promote rearrangement of a number of *N*-Boc or *N*-Cbz *O*-(halo-4-nitrophenyl)hydroxylamines (Table 1).<sup>4</sup> In some cases, where the yield of the *N*-hydroxyaniline was poor, starting material was recovered. We note also that most of the *N*-hydroxyanilines are not stable (**8**, **10** and **12** were the worst). When stored at ambient temperature, open to the air, these materials became black tars. The instability of some of the products could also contribute to the poor yield.



## Figure 1.

Potential intra- and intermolecular reaction transition states are shown in Fig. 1. A crossover experiment was run to determine whether this reaction is intra- or

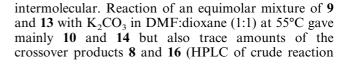
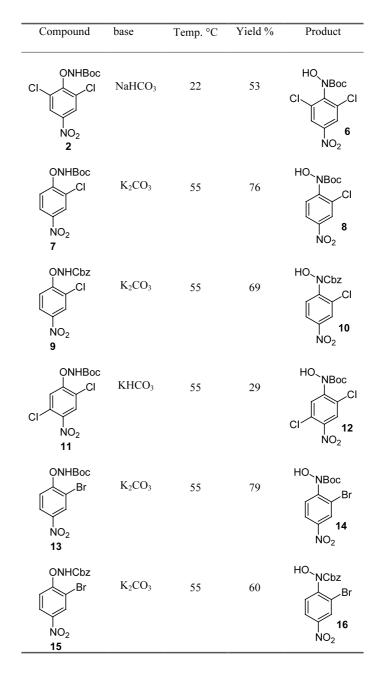


Table 1. Reaction of O-(halo-4-nitrophenyl)hydroxylamines with base



with confirmation by LC/MS) in mixture а 63.3:35.4:0.30:1.0 ratio (10:14:8:16). The fact that any crossover was observed indicates that an intermolecular reaction pathway is occurring. A rationale for the very small proportion of crossover products may suggest a minor reaction pathway. Alternatively, intermolecular displacement could be due to initial DMF activation/ displacement of the -ONHCO<sub>2</sub>R group. When DMA is substituted for DMF, the reaction rate and yield is virtually identical to that of the DMF reaction. Additionally, benzyl N-hydroxycarbamate (HONHCO<sub>2</sub>Bn) was not found in the crude reaction mixture (HPLC, HPLC/MS) of the crossover experiment nor in the rearrangement of 9 (HPLC, HPLC/MS, TLC). This is evidence for the reaction not occurring simply by displacement.

Many attempts were made to use 2 as an electrophilic N-Boc amine source to prepare substituted hydrazines.<sup>5</sup> Amine nucleophiles or salts of imides reacted with 2 to give mainly hydroxyaniline 6. We were able to obtain N,N-dibenzyl-N'-Boc hydrazine (18)<sup>6</sup> in 43% yield by reaction of 2 with dibenzylamine (Eq. (1)); but this seems to be the exception rather than the rule.

 $\begin{array}{c|c} & ONHBoc & dioxane \\ Bn, & Cl & Cl & DMF (1;1) & Bn, \\ NH & + & 55 \ ^{\circ}C & Bn' \\ NO_2 & 43\% \end{array}$ (1) 17 6 18

In conclusion, we have described reactions of some O-(halo-4-nitrophenyl)hydroxycarbamates with bases to provide the *N*-hydroxyanilines in modest yield and that the *N*-hydroxyanilines are not stable under ambient conditions. To our knowledge, this is the first occasion of such a report.<sup>7</sup> Crossover experiment has shown that the reaction could be both inter- and intramolecular in nature. Reagent **2** was shown to be a suitable aminating agent for dibenzylamine. Additional work exploring the use and reactivity of reagent **2** under a variety of conditions and with other substrates will be reported in due course.

## Acknowledgements

The authors would like to thank D. Dejohn for the HRMS data and Professor Andy Myers, Drs. D. Belmont, J. Davidson and D. Pflum for helpful discussions and suggestions.

## References

 Boc cleavage in these systems has been accomplished with TFA, HCl, HCO<sub>2</sub>H, or HClO<sub>4</sub>. See: (a) Seradsky, T.; Salemnick, G.; Nir, Z. *Tetrahedron* **1972**, *28*, 3833–3843; (b) Tamura, Y.; Minamikawa, J.; Ikeda, M. Synthesis **1977**, 1–17.

- Boyles, D. C.; Curran, T. T.; Parlett, R. V.; Davis, M.; Mauro, F. Chem. Process Res. Dev. 2002, 6, 230–233.
- 3. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 187371.
- 4. The below experiments are representative of the preparation of the hydroxylamines and the *N*-hydroxyanilines. All compounds were characterized by <sup>1</sup>H NMR, IR, MS, and HRMS or CHN.

Preparation of 2: A solution of t-butyl-N-hydroxycarbamate (6.1 g, 45 mmol) and 1 M KOH in IPA (80 mL) in IPA (65 mL) was cooled to -20°C and treated dropwise over 30 min with a solution of 1,2,3-trichloro-5-nitrobenzene (10 g, 44 mmol) in THF (140 mL). The resulting red solution was stirred at -20 for 3.5 h. The resulting reaction mixture was judged complete by TLC (EtOAc/hexanes, 1:4) and quenched with 1 M citric acid (120 mL) and allowed to warm to rt. The mixture was diluted with H<sub>2</sub>O (150 mL) and EtOAc (300 mL). The organic phase was separated and washed with brine (2×100 mL), dried (MgSO<sub>4</sub>), filtered and filtrate concentrated in vacuo. The resulting solid was purified by flash chromatography using EtOAc/hexanes (1:4) to provide 9.36 g of 2 in 66% yield. Data for 2: <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  11.4 (s, 1H), 8.30 (s, 2H), 1.38 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  157, 156, 145, 130, 125, 84.1, 28.3; IR (neat):  $v_{\text{max}}$  3298, 3095, 1732, 1530, 1349 cm<sup>-1</sup>. Anal. calcd for C<sub>11</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>5</sub>: C, 41.11; H, 3.58; N, 8.52. Found: C, 40.89; H, 3.74; N, 8.67%.

Base-promoted rearrangement of 2: preparation of 6: A solution of 2 (1 g, 3.1 mmol) in DMF and dioxane (8 mL each) was treated with NaHCO<sub>3</sub> (anhydrous, 0.31 g, 3.7 mmol) and stirred at rt for 18 h. The reaction mixture was treated with 2 M HCl (15 mL), diluted with H<sub>2</sub>O (75 mL) and EtOAc (75 mL). The organic phase was separated and washed with  $H_2O$  (2×25 mL), then dried (MgSO<sub>4</sub>), filtered and filtrate concentrated in vacuo. The resulting material was purified by flash-column chromatography on SiO<sub>2</sub> using EtOAc/hexanes (1:1). The resulting solid was recrystallized from TBME/hexanes (1:3) to give 530 mg, 53% yield. This material also proved suitable for X-ray crystal structure determination. Data for 6: <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  10.6 (s, 1H), 8.38 (s, 2H), 1.29 (s (broad), 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  155, 148, 142, 137, 124, 84.4, 28.2; IR (neat):  $v_{\text{max}}$  3212, 3103, 2984, 1701, 1533, 1341 cm<sup>-1</sup>. Anal. calcd for C<sub>11</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>5</sub>: C, 41.11; H, 3.58; N, 8.52. Found: C, 40.93; H, 3.61; N, 8.49%. APCI HRMS (MeCN/H<sub>2</sub>O) m/e 321.0046 ( $C_{11}H_{12}Cl_2N_2O_5$ -H requires m/e 321.0045).

- Imide 5 was tried with or without base. Diethylamine, 4-methoxyaniline, and substituted benzylamines were reacted with 2 with the intent to N-aminate. Predominant conversion of 2 into hydroxyaniline 6 was observed.
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- As pointed out to us by a referee, a [2,3]-sigmatropic rearrangement of *N*-lithio-*N*-benzyl-*O*-allylhydroxylamines has been reported which is somewhat related. See: Davies, S. G.; Jones, S.; Sanz, M. A.; Teixeira, F. C.; Fox, J. F. *Chem. Commun.* **1998**, 2235–2236.