



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

David C. Boyles, Timothy T. Curran,* Derek Greene, Dainius Macikenas† and Roger V. Parlett, IV

Pfizer Global Research and Development, Pharmaceutical Sciences, 2800 Plymouth Road, Ann Arbor, MI 48105, USA

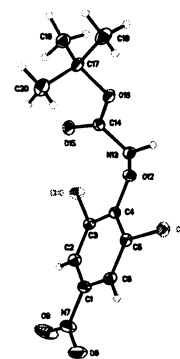
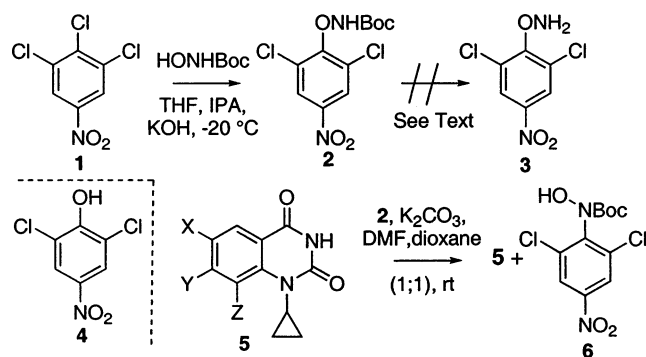
Received 27 June 2002; accepted 22 July 2002

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 (NaHCO₃ or K₂CO₃) 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-NO₂-phenyl)hydroxylamine was also found to *N*-Boc aminate Bn₂NH to form the protected hydrazine in modest yield. © 2002 Elsevier Science Ltd. All rights reserved.

During the course of the preparation of various *O*-(4-nitrophenyl)hydroxylamines as electrophilic aminating agents, we attempted to prepare *O*-(2,6-dichloro-4-nitrophenyl)hydroxylamine **3** by Boc cleavage of **2** (Scheme 1). We were not able to prepare this material by normal means,¹ and only isolated phenol **4**. An attempt was made to aminate imide **5** by reaction with *N*-Boc **2** under our standard aminating conditions.² 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-

hydroxyaniline **6** (unambiguously established by single-crystal X-ray analysis;³ 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)hydroxylamines¹ was explored using 1.5



X-Ray Crystal
Structure of **6**

Scheme 1.

* Corresponding author. Fax: 734-622-3294; e-mail: timothy.curran@pfizer.com

† Author to whom questions concerning the X-ray crystal structure should be addressed.

equiv. of K_2CO_3 , $NaHCO_3$, or $KHCO_3$ 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).⁴ 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.

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

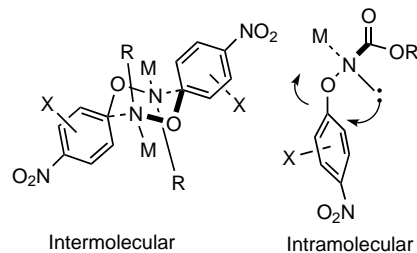


Figure 1.

intermolecular. Reaction of an equimolar mixture of **9** and **13** with K_2CO_3 in DMF:dioxane (1:1) at 55°C gave mainly **10** and **14** but also trace amounts of the crossover products **8** and **16** (HPLC of crude reaction

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

Compound	base	Temp. °C	Yield %	Product
 2	$NaHCO_3$	22	53	 6
 7	K_2CO_3	55	76	 8
 9	K_2CO_3	55	69	 10
 11	$KHCO_3$	55	29	 12
 13	K_2CO_3	55	79	 14
 15	K_2CO_3	55	60	 16

