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A Practical Synthesis of Substituted Benzo[c]cinnoline-N,N'-dioxides and N-oxides.

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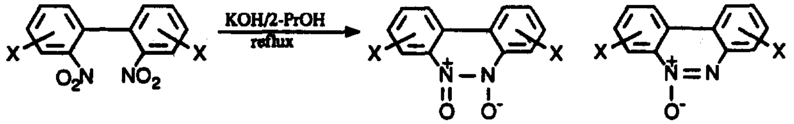
Abstract. *A practical synthesis of variously substituted benzo[c]cinnoline-N,N'-dioxides and N-oxides is described, based on the reduction of the appropriate o,o'-dinitrobiphenyl compound with KOH in refluxing 2-propanol.*

Reductive cyclization of *o,o'*-dinitrobiphenyls provides access to the benzo[c]cinnoline skeleton.[1] Reductants previously used include $LiAlH_4$, Na/Hg in MeOH, Zn in alkaline aqueous EtOH, Na_2S in aqueous EtOH, Ph_3P in alkaline EtOH, hydrazine with Ra-Ni in EtOH, H_2 with Ra-Ni in alkaline EtOH.[1] More recently $(PhTe)_2/NaBH_4$[2] and Sm[3] have also been used. The stage of reduction achieved, corresponding to the *N,N'*-dioxo-, the *N*-oxo- or the benzo[c]cinnoline products, depends on the conditions used. While attainment of benzo[c]cinnolines in good yields is readily achieved, the same is not generally true for the *N,N'*-dioxide and *N*-oxide, most methods leading to mixtures of products.

We report in this paper that the low-cost and easily available and handled system, KOH/2-propanol, can be conveniently used to perform reductive cyclization of *o,o'*-dinitrobiphenyls to the *N,N'*-dioxide or *N*-oxide stages (Table 1).[4] The data suggest that the reaction proceeds in a stepwise fashion, in agreement with earlier proposals, and that the first stage is faster than the second. Thus, the use of low base concentrations and short reaction times allows one to stop the reduction of **1a** to **2a** (isolated in 64% yield). Higher concentrations of base and longer reaction times lead to isolation of the *N*-oxide **3a** in 77% yield. Compound **1b** is activated for nucleophilic substitution via the addition/elimination (S_NAr) reaction. Nitro reduction is, however, faster than Cl-substitution so that by an appropriate choice of the reaction conditions the new chloro-substituted benzo[c]cinnoline-*N,N*-dioxide **2b** could be synthesized in good yield. On the other hand, the substitution product, the new 5,5'-diisopropoxy-2,2'-dinitrobiphenyl **1e**, was obtained from the reaction of **1b** in the presence of a tetraalkylammonium salt and at a temperature slightly below that of reflux.[5]

Table 1. Reductive Cyclization of *o,o'*-Dinitrobiphenyls **1a**-**1e** with KOH in Refluxing 2-Propanol



1a-e **2a-e** **3a-e**

Substrate^{a}	X	KOH equivalents	Reaction time (h)	Products^{6} (%-yield)^{b}	
1a	H	2	2	**2a** (64)	
1a	H	4	7		**3a** (77)
1b	5,5'-Cl_2	2	0.33	**2b** (67)	
1b	5,5-Cl_2	10^{c}	4.5	**1e** (67)	
1c	4,4'-$(CH_3)_2$	10	0.5	**2c** (65)	**3c** (15)
1c	4,4'-$(CH_3)_2$	10	4.5		**3c** (72)
1d	4,4'-$(CF_3)_2$	2	0.25		**3d** (55)
1e	5,5'-(2-PrO)$_2$	10	2	**2e** (68)	

[a] The substrate concentration was 0.03M. [b] Isolated yields after purification via column chromatography. [c] Reaction carried out at 75°C with 10 equiv. of Me_4NCl.

Electron-withdrawing substituents provoke an increase in reactivity with respect to the unsubstituted model **1a**, whereas more drastic conditions are required for the reaction of the CH_3- and the 2-PrO-substituted compounds, **1c** and **1e**. This reactivity trend is in keeping with the notion that the base-induced reduction of aromatic nitrocompounds involves anionic intermediates.[7]

References and Notes

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4. A typical procedure is as follows. **2a**: to a solution of **1a** (0.506g, 2mmol) in 2-propanol (40ml) at reflux are added 20ml of a 2-propanol solution of KOH (0.23g, 4mmol). The mixture is kept at reflux for 2 hours and, after cooling, is poured into water and neutralized. After separation of the precipitate the aqueous layer is extracted with $CHCl_3$. The precipitate plus the residue from the organic layer after evaporation of the solvent are subjected to low-pressure chromatography (silica, chloroform/ethyl acetate: 15/1) to yield **2a** (0.28g, 64% yield) and **3a** (0.045g, 11% yield).
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