Pergamon

Tetrahedron Letters 41 (2000) 3519–3522

TETRAHEDRON LETTERS

Specific *para*-hydroxylation of nitronaphthalenes with cumene hydroperoxide in basic aqueous media

Lei Zhu and Lin-hua Zhang *

Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, CT 06877-0368, USA

Received 28 February 2000; accepted 8 March 2000

Abstract

A synthetic method for specific *para*-hydroxylation of nitroarenes has been developed. The reaction of nitronaphthalenes with cumeme hydroperoxide in basic aqueous media produces exclusively *para*-hydroxy nitronaphthalenes in good yield. The selectivity of *ortho* and *para* hydroxylation is mediated by water content. The rationale for water-controlled orientation of hydroxylation has been briefly discussed. © 2000 Elsevier Science Ltd. All rights reserved.

Interest in the nucleophilic substitution of hydrogen in nitroarenes has grown significantly in recent years.[1] The hydroxylation of nitroarenes with potassium peroxide (K_2O_2) in liquid ammonia yielded mono- or dinitronaphthols. The product ratio of *ortho*- and *para*-substitution is temperature dependent.[2] The hydroxylation of nitroarenes with alkyl hydroperoxide was also reported in which the position of hydroxylation depended on what base was selected.[3] It was reported that the hydroxylation of nitronaphthalene with organic peroxides in DMSO generated only *para*-isomer although the isolation was not described.[4,5] However, in our hands the reported procedure[3–5] resulted in a complex mixture, and the ratio of *para*-nitronaphthol to *ortho*-nitronaphthol was about 87 to 13 in DMSO by HPLC analysis. The separation of the *para*-isomer from the *ortho* is very tedious and needs chromatography. Another way of making *para*-alkoxynitronaphthalenes by a nitration of naphthalene was reported, but the reaction yielded a mixture of regioisomers that was not easy to purify.[6] Apparently, there is a need to develop a reproducible and scaleable method to prepare the *para*-hydroxy isomer from the nitroarenes. The present study reports a synthetic route, amenable to large scale, to *para*-hydroxylation of 1-nitro or 1,5-dinitro naphthalene through the nucleophilic substitution of the hydrogen.

We first studied the hydroxylation of nitronaphthalene with organic peroxides in DMSO and DMF. The results were not satisfactory in our hands due to the formation of *para*- and *ortho*-isomers. We then examined the reactivity difference between cumene hydroperoxide and hydrogen peroxide as the hydroxylation agents. The technical grade of cumene hydroperoxide works well in our hands without further purification. However, hydroxylation of nitroarenes with hydrogen peroxide did not proceed as

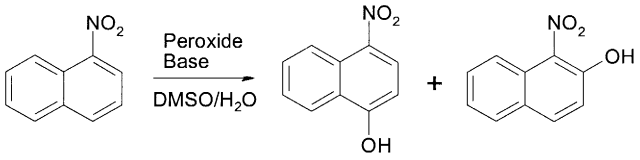
* Corresponding author.

PII: S0040-4039(00)00415-9

smoothly as with cumene hydroperoxide due to the precipitation of starting material from the reaction mixture. In an attempt to achieve a homogeneous reaction condition, a small amount of water was introduced into the DMSO solution. To our surprise, the hydroxylation of nitroarenes proceeds much better than in DMSO alone. Apparently, this reaction does not need strictly controlled anhydrous conditions as previously reported.[2]

On the basis of this discovery, we started our research on hydroxylation of nitroarenes in a mixture of water and DMSO. As shown in Table 1, the reaction took place very slowly in water due to the insolubility of the starting materials. When the reaction was carried out in anhydrous DMSO, a mixture of *para*- and *ortho*- regioisomers was formed which was contradictory to previous reports. However, in a mixture of water (25%) and DMSO (75%), this nucleophilic substitution gave exclusively the product of *para*-hydroxylation in 62–82% yield as illustrated in Table 1.

Table 1
Hydroxylation of 1-nitronaphthalene



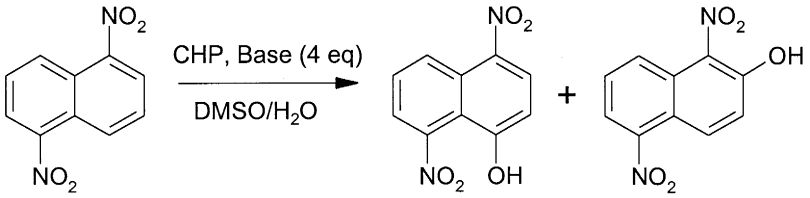
Base	Peroxide	Solvent	Time (h)	*Ortho*- Isomer (%)	*Para*- Isomer (%)
KOH (4 eq)	CHP* (1.0 eq)	H_2O	10	0	2
KOBu (t) (4 eq)	CHP (0.8 eq)	DMSO (anhydrous)	1	4	26
KOH (4 eq)	CHP (1.0 eq)	DMSO (anhydrous)	2	3	46
KOH (4 eq)	CHP (0.8 eq)	DMSO/H_2O (75/25%)	2	0	62
KOH (4 eq)	CHP (1.0 eq)	DMSO/H_2O (75/25%)	2	0	73**
KOH (4 eq)	CHP (1.0 eq)	DMSO/H_2O (75/25%)	2	0	82***
KOH (4 eq)	H_2O_2 (3.0 eq)	DMSO/H_2O (75/25%)	24	0	30

* CHP: cumene hydroperoxide. **Added mixture of starting material and peroxide into the base solution.
***Added peroxide into the basic solution of starting material.

These reaction conditions were also tested on 1,5-dinitronaphthalene, which was reported among the most unsuccessful ones to achieve *para* substitution due to steric hindrance by the substituent at position 5.[1,7] It was also illustrated that the regio-preference varies with the base. Interestingly, under our aqueous conditions hydroxylation predominantly took place at the *para*-position of 1,5-dinitro naphthalene showing strong evidence of stereo- and base-independence (Table 2). When the water content increased to 25%, the *para*-isomer became the sole product. Further studies revealed that water played an important role in controlling the regiochemistry, and also improved the reaction yield as shown in Table 2.

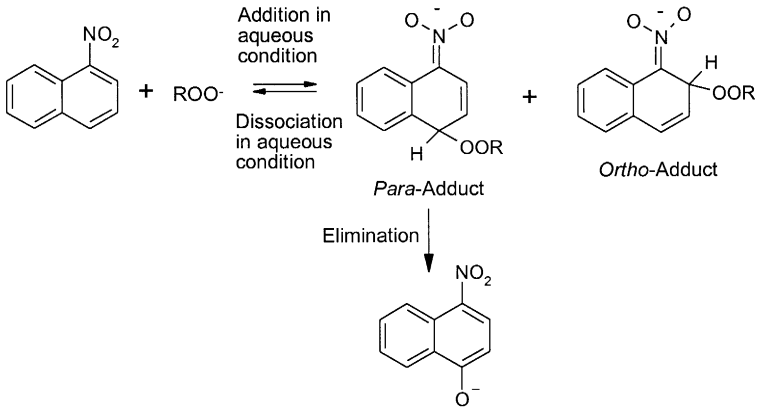
The nucleophilic substitution of nitroarenes in aqueous media provides an economic and scaleable route to *para*-isomers, which also sheds some light on the reaction mechanism. It is generally accepted that *ortho*-addition is kinetically more favorable than *para*-addition in nitroarenes, but the *para*-adduct

Table 2
Hydroxylation of 1,5-dinitronaphthalene



Water (%) in DMSO	Base	Time (h)	*Ortho*-Isomer (%)	*Para*-Isomer (%)
Anhydrous	NaOH	2	5	30
10	NaOH	4	2	50
20	NaOH	4	0.5	70
25	NaOH	4	0	80
25	KOH	10	0	83
25	KOBu(t)	10	0	70
50	NaOH	10	0	25
67	NaOH	10	0	1

intermediate is thermodynamically more stable than *ortho*-isomer.[7] However, the conditions for converting *ortho*-adduct to *para*-adduct through thermodynamic equilibrium have not been reported. Our results revealed that the *ortho*- to *para*-adduct conversion could be facilitated by water content possibly through a reversible process (Scheme 1). Another possible explanation is that water solvates change the reaction kinetics, and make the *para*-substitution kinetically more favorable.



Scheme 1.

In summary, in basic aqueous media the nucleophilic hydroxylation of nitroarenes leads exclusively to the *para*-isomer, which provides an economical and scaleable route to these series of compounds that are not easily available through aromatic electrophilic substitution. The mechanism that directs the regiochemistry is worthy of further study.

General procedure: 1-nitronaphthalen (1.0 mol) was dissolved in DMSO (1.5 L). Under cooling, KOH (4.0 mol) in H_2O (0.5 L) was added. With stirring, a solution of cumene hydroperoxide (tech. Grade, 1.0 mol) in DMSO (0.25 L) was added, and the pot temperature was controlled below 30°C. After addition the reaction was stirred at room temperature for 2 h, and the aqueous solution of $Na_2S_2O_3$ (30 g in 120

g water) was added. After 1 h, H_2O (1.5 L) and EtOAc (1.2 L) was added. The pH of the solution was adjusted to about 4 with HCl (c) while keeping the solution below 5°C. The layer was separated, and the aqueous layer was extracted with EtOAc (0.5 L). The combined EtOAc layers were washed with 10% NaCl solution (2×0.5 L). Sufficient 20% aqueous NaOH was added to adjust the pH to about 10 at low temperature. The aqueous layer was separated and washed with EtOAc (2×0.5 L). With cooling and stirring, hydrochloric acid (c) was slowly added to aqueous solution until about pH 4. The solid was collected and dried under vacuum to a constant weight. The structures of the products were confirmed by comparison to authentic samples.[1]

References

1. Makosza, M.; Sienkiewicz, K. *J. Org. Chem*. **1998**, *63*, 4199. Francoise, R.-M.; Eric, R. *Cur. Org. Chem.* **1999**, 445. Golinski, J.; Makosza, M. *Tetrahedron Lett.* **1978**, 3495. Lawrence, N. J.; Lamarche, O.; Thurrab, N. *Chem. Commun.* **1999**, 689. Meisenheimer, J.; Patzig, E. *Ber. Deutch. Chem. Ges*. **1906,** 39, 2533. Price, C. C.; Voong, S.-T. *Organic Synthesis* Wiley: New York, 1955; Coll. Vol. 3, p. 664. Makosza, M.; Bialecki, M. *J. Org. Chem.* **1992**, *57*, 4784. Seko, S.; Kawamura, N. *J. Org. Chem.* **1996**, *61*, 442. Pagoria, P. F.; Mitchell, A. R.; Schmidt, R. D. *J. Org. Chem.* **1996**, *61*, 2934. Katritzky, A. R.; Laurenzo, K. S. *J. Org. Chem.* **1986**, *51*, 5039; **1988**, *53*, 3978. Gitis, S. S.; Glaz, A. I.; Grigoriev, B. B.; Kaminsky, A. Y.; Martynienko, A. S.; Saukov, P. I. *Zh. Org. Khim.* **1967**, *3*, 1617.
2. Malykhin, E. V.; Shteingarts, V. D. *Russ. J. Org. Chem*. **1997**, *3*, 636.
3. Makosza, M.; Sienkiewicz, K. *J. Org. Chem.* **1990**, *55*, 4979.
4. Mattersteig, G.; Pritzkow, W.; Voerckel, V. *J. Prakt. Chem*. **1990**, *4*, 569.
5. Brose, T.; Holzscheiter, F.; Mattersteig, G; Pritzkow, W.; Voerckel, V. *J. Prakt. Chem*. **1992**, *334*, 497.
6. Mellor, J. M.; Parkes, R. *Tetrahedron Lett*. **1997**, *38*, 8739.
7. Makosza, M.; Kwast, A. *J. Phys. Org. Chem*. **1998**, 341.