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NEW PREPARATION OF *o*-ARYLOXYPHENOLS VIA CYCLOHEXENONE OXIDES

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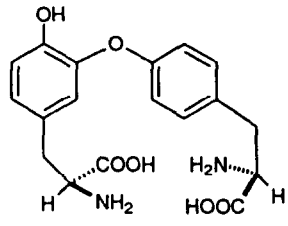
Summary: Reaction of cyclohexenone oxides with phenols under basic two-phase conditions with sonication followed by oxidation represents a new, efficient two-step synthesis of *o*-aryloxyphenols.

O-Aryloxyphenols have been shown to possess strong antimicrobial and antibacterial activity.[2] They are also an important structural unit in an ever-increasing number of antibiotics derived from isodityrosine **1**,[3] e.g., K-13 **2**[4] and piperazinomycin **3**,[5] among others. Despite a large amount of synthetic effort in this area,[6] there is still a need for short and efficient syntheses of *o*-aryloxyphenols and their derived antibiotics. We report herein a useful two-step preparation of these compounds from readily available materials.



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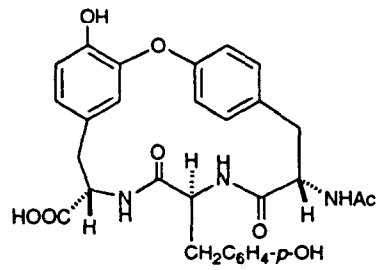

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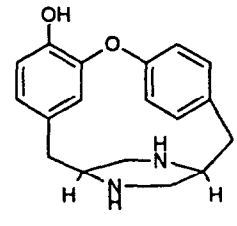

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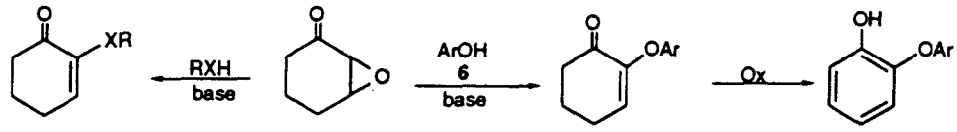
It has been known for some time that nucleophilic attack, e.g., with thiols and amines, on cyclic epoxy ketones occurs at the α-carbon to give after dehydration, the 2-alkylthio or 2-aminoenone.[7] We reasoned that if this reaction could be made to work well with phenols on simple epoxycyclohexanones, then a final dehydrogenation would give the desired *o*-aryloxyphenols.

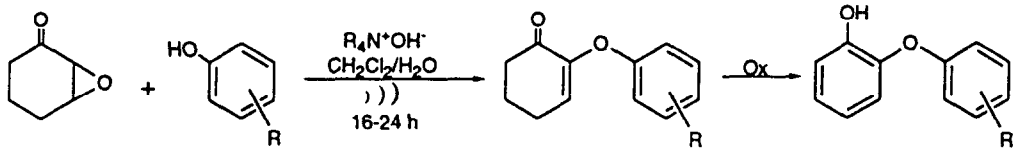
Although cyclohexenone oxide **4** is readily converted into 2-heterosubstituted cyclohexenones **5** (X=S,NR) with good nucleophiles such as thiols and amines,[7] the corresponding reaction with alcohols or phenols affords little or no product **5** (X=O). Schultz successfully used this reaction to prepare 3-substituted 2-aryloxy cyclohexenones for use in his photoarylation process.[8] However, he found that vigorous reaction conditions were necessary for the phenolic substrates (potassium hydride in refluxing THF and HMPA) and no β-unsubstituted epoxy ketones were



5 X = O, S, NH 4 7 8

investigated.[8] Subjection of **4** to these conditions resulted in decomposition of both starting material and product. Similarly, the reaction of the anions of phenols **6** with **4** in aqueous ethanol or in dry THF gave poor yields of the desired α-aryloxy enones **7**. We have found that the use of a tetraalkylammonium hydroxide base in the two-phase system, water and CH_2Cl_2, provides conditions mild enough to protect the labile cyclohexenone oxide while being basic enough to promote nucleophilic attack by phenols.[9] Sonication of the reaction mixture gave the desired 2-aryloxycyclohexenones **7** in 44-79% isolated yield from **4** (Table 1). The chiral center in phenol **6c** (methyl *N*-benzoyl-L-tyrosinate) was not lost in this process, giving the optically active tyrosine derivative **7c** in 79% purified yield.

Table 1: Preparation of *o*-Aryloxyphenols 8 from Cyclohexenone Oxide 4



4 6 7 8

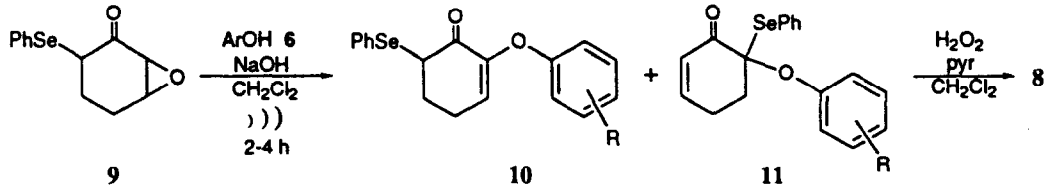
Phenol	Yield of 7	Yield of 8	Overall (from 6)
6a R = H[a]	48%	46%	22%
6b R = 4-OMe[a]	69%	32%[c]	22%
6c R = 4-$CH_2CH(CO_2Me)NHBz$[a]	79%	34%[d]	27%
6d R = 2-OMe[b]	44%	60%	26%
6e R = 3-Me[b]	50%	49%	25%
6f R = 4-Me[b]	65%	48%	31%

a) $R_4NOH = Et_3NBnCl$ with NaOH b) $R_4NOH = Me_4NOH$ c) isolated as the charge-transfer complex with benzoquinone d) $CuBr_2/LiBr/CH_3CN$ oxidation

A two-step procedure for oxidation of the aryloxyenones was utilized. Formation of the 2-silyloxy diene, followed by oxidation with Pd(II) acetate gave the *o*-aryloxyphenols **8** in moderate yields.[10] We were unable to prepare the silyl enol ether of tyrosine derivative **7c**, however, so this substrate was aromatized with cupric bromide and lithium bromide in refluxing acetonitrile[11] to give **8c** in 34% yield but with no significant loss of optical activity.

Aiming to improve upon the difficult dehyrogenation step, we prepared the known 6-(phenylseleno)cyclohexenone oxide **9**.[12] If this derivative participated in the coupling reaction, the subsequent oxidation and elimination to the phenol should be facile. Modified reaction conditions were developed, namely a nonaqueous, two-phase system of

Table 2: Preparation of *o*-Aryloxyphenols 8 from (Phenylseleno)epoxide 9

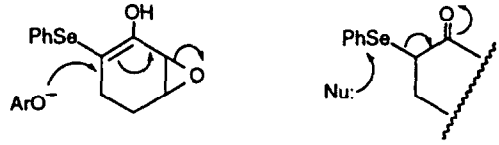


9 10 11

Phenol	Yield of 10	Yield of 11	Yield of 8	Overall (from 6)
6a R = H	36	6	91%	38%
6b R = 4-OMe	46	0	99%	45%
6c R = 4-$CH_2CH(CO_2Me)NHBz$	26	3	99%[a]	28%
6d R = 2-OMe	30	0	92%	28%
6e R = 3-Me	33	15	87%	43%
6f R = 4-Me	47	5	99%	51%

a) mCPBA oxidation

solid sodium hydroxide in CH_2Cl_2.[13] These conditions gave good yields of the 6-(phenylseleno)-2-aryloxycyclohexenones **10** along with minor amounts of the 6-(phenylseleno)-6-aryloxycyclohexenones **11** (Table 2). These latter compounds are presumably produced via 1,4-addition of the phenols to the vinyl oxirane **12**, formed by enolization of the ketone in **9** due to the increased acidity of the α-proton.[14] Analysis of the product mixture also revealed several minor deselenated products, most likely arising from nucleophilic attack on selenium as shown in **13**. Shorter reaction times helped to minimize this deselenation. The steric bulk of the selenium is reflected in the lower yield of the guaiacol **10d** while the disappointingly low yield of the tyrosine substrate is most likely due to solubility problems.



12 13

Treatment of either the 1,2- or 1,4-products **10** or **11** with excess hydrogen peroxide and pyridine in CH_2Cl_2 provided quantitative conversion to the corresponding 2-aryloxyphenols **8**. As expected, this oxidation is quick (proceeding in one hour at 25 °C), reliable and easy. For the tyrosine derivatives, **10c** and **11c**, the use of peracid (e.g., mCPBA) gave a better yield of **8c** (99%).

Thus in only two steps, nucleophilic displacement and oxidation, one can prepare *o*-aryloxyphenols from α-(phenylseleno)cyclohexenone oxide in good overall yield. The further use of this process for the synthesis of isodityrosine and its derived antibiotics is currently underway in our laboratories.

Acknowledgment: We thank the National Institutes of Health (GM 31349) for generous financial support.

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9) The phenol **6** was added to a solution of ammonium hydroxide (1 eq) in water and the mixture sonicated for 15 min. A solution of the epoxide **4** in CH_2Cl_2 was added and the two-phase mixture sonicated for 16-24 h. The product was extracted from the mixture with CH_2Cl_2 and purified by column chromatography.

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13) The phenol **6** was added to solid sodium hydroxide (1 eq) in CH_2Cl_2 and the mixture sonicated for 15 min to give a milky suspension. A solution of the epoxide **4** in CH_2Cl_2 was added and the two-phase mixture sonicated for 16-24 h. Aqueous NH_4Cl was added and the reaction worked up as in reference 9 above.

14) For similar conjugate additions to enol ethers of cyclohexenone oxides, see: Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114.

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