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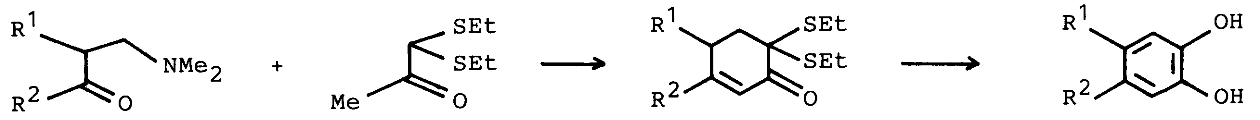
A NEW ENTRY TO 1,2-BENZENEDIOL CONGENERS

Yutaka OZAKI, Ikumi OSHIO, and Sang-Won KIM*
Faculty of Pharmaceutical Sciences, Josai University, Keyakidai, Sakado, Saitama 350-02, Japan

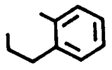
1,2-Benzenediols and their monoethers were efficiently prepared from α,α-bis(ethylthio)cyclohexenones which were constructed by the C3+C3 annulation of 1,1-bis(ethylthio)propan-2-one and the Mannich bases.

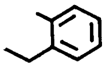
KEYWORDS 1,2-benzenediol; aromatic synthesis; annulation; aromatic compound; acetal

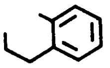
Formation of various phenolic compounds from aliphatic sources has been investigated extensively owing to some synthetic advantages.[1)] However, no effective preparation of 1,2-benzenediols and their monoethers from aliphatic compounds has been proposed in the literature. Supplying of 1,2-benzenediols is of significance in synthetic chemistry because numerous biologically active and naturally occurring compounds have the structure in their framework.[2)] In addition, the regioselective preparation of the aromatic systems is in demand not only to supply the compounds but also for structural studies. In the course of our study on synthesis of benzenoid aromatic rings such as 1,3-benzenediols and 1,2,4-benzenetriols,[3)] a systematic construction of 1,2-benzenediols was gained accompanied with a regioselective synthesis of their monoethers. We here describe a new regiocontrolled route to the title compounds by the annulation reaction followed by aromatization.



1 **2** **3** **4**

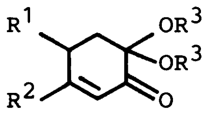
1	R^1	R^2
a	$-(CH_2)_3-$	
b	$-(CH_2)_4-$	
c	$-(CH_2)_5-$	
d	H	Ph
e		

3	R^1	R^2	
a	$-(CH_2)_3-$		(49%)
b	$-(CH_2)_4-$		(76%)
c	$-(CH_2)_5-$		(78%)
d	H	Ph	(69%)
e			(62%)

4	R^1	R^2	
a	$-(CH_2)_3-$		(20%)[7a]
b	$-(CH_2)_4-$		(27%)[7b]
c	$-(CH_2)_5-$		(41%)[7c-e]
d	H	Ph	(54%)[7f]
e			(67%)

The 1,2-benzenediols (**4a-e**) were prepared via the α,α-bis(ethylthio)cyclohexenones (**3a-e**) which were obtained from the C3+C3 annulation as follows. The Mannich bases (**1a-e**) and 1,1-bis(ethylthio)propan-2-one (**2**)[3b,3c,4)] were employed as each of the C3 sources. The former, provided from the corresponding ketones, are regarded as the precursor of the α-methyleneketones.[5)] The latter is equivalent to the α-diketone "$-CH_2-CO-CO-$" which is converted to the geminated phenolic hydroxyl groups on the last stage of the aromatic ring formation. The annulation reaction of **1a-e** (1.0 equiv.) with **2** (1.0 equiv.) in the presence of sodium hydride (0.3 equiv.) in dimethoxyethane gave the cyclohexenones (**3a-e**).

Dethioacetalization of **3a-e** with mercuric perchlorate [Hg(ClO$_3$)$_2$ 3H$_2$O]6) in CHCl$_3$-THF at room temperature gave carbonyl compounds, which were heated with acetic acid under reflux to give the 1,2-benzenediols (**4a-e**). Thus, an efficient route to 1,2-benzenediols was exploited via the C3+C3 annulation.



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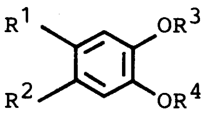
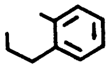
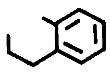
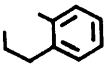
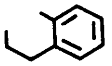
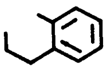
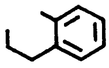
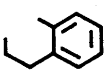
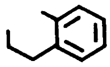


6

5	R^1	R^2	R^3	
a	-(CH$_2$)$_3$-		Me	(55%)
b	-(CH$_2$)$_4$-		Me	(72%)
c	-(CH$_2$)$_5$-		Me	(57%)
d	H	Ph	Me	(82%)
e			Me	(35%)
f	-(CH$_2$)$_3$-		Et	(43%)
g	-(CH$_2$)$_4$-		CH$_2$Ph	(34%)
h	H	Ph	CH$_2$Ph	(29%)
i			CH$_2$Ph	(33%)
j	H	Ph	CH$_2$CH=CH$_2$	(26%)
k			CH$_2$CH=CH$_2$	(46%)

6	R^1	R^2	R^3	R^4	
a	-(CH$_2$)$_3$-		Me	H	(53%)8a
b	-(CH$_2$)$_4$-		Me	H	(52%)8b
c	-(CH$_2$)$_5$-		Me	H	(77%)7d,8c
d	H	Ph	Me	H	(51%)8d
e			Me	H	(48%)
f	-(CH$_2$)$_3$-		Et	H	(57%)
g	-(CH$_2$)$_4$-		CH$_2$Ph	H	(67%)
h	H	Ph	CH$_2$Ph	H	(79%)
i			CH$_2$Ph	H	(88%)
j	H	Ph	CH$_2$CH=CH$_2$	H	(68%)
k			CH$_2$CH=CH$_2$	H	(77%)
l	H	Ph	H	Me	(63%)8d
m	H	Ph	CH$_2$Ph	Me	(99%)
n			H	Me	(80%)
o			CH$_2$Ph	Me	(96%)

The 1,2-benzenediol monoethers are interesting and important compounds because of the abundance of the naturally occurring compounds which have the same partial structure, but the regioselective construction of the monoethers has rarely been reported. The annulated compounds (**3a-e**) were available for the preparation of the monoethers. Modification of the reaction condition used for the above dethioacetalization gave the synthetic intermediates (**5**) suitable for the formation of the 1,2-benzenediol monoethers (**6a-k**). The **3a-e** was deacetalized in the presence of methyl alcohol with the same reagent, mercuric perchlorate. The acetals (**5a-e**) were obtained as a result of the transacetalization. Treatment of **5a-e** in refluxing acetic acid for 1 h gave the 1,2-benzenediol monomethyl ethers (**6a-e**). It is clear that the methoxyl group of these aromatic compounds came from the methyl alcohol used in the dethioacetalization reaction.

Several monoethers (**6f-k**) were prepared via the acetals (**5f-k**) which were obtained from the thioacetals (**3a-e**) using ethyl alcohol, benzyl alcohol, and allyl alcohol in the similar manner as noted for the monomethyl ethers. Successful preparation of these monoethers demonstrated that the origins of the alkoxyl groups on the aromatic rings were the corresponding alcohols employed in the transacetalization.

The isomeric counterpart (**6l**) of the monomethyl ether (**6d**) was synthesized from the monobenzyl ether (**6h**). Methylation of the ether (**6h**) with dimethyl sulfate in the presence of potassium carbonate in acetone gave the monobenzyl monomethyl ether (**6m**). Debenzylation of **6m** by catalytic reduction afforded the monomethyl ether (**6l**). The monomethyl ether **6n**, the isomeric counterpart of **6e**, was also obtained from **6i** via **6o** in the a similar manner. Thus the regioselective preparation of pairs of isomeric monomethyl ethers was accomplished unambiguously.

In conclusion, 1,2-benzenediols (**4**) were prepared from α,α-bis(ethylthio)cyclohexenones (**3**) which were readily obtained from the Mannich bases (**1**) and 1,1-bis(ethylthio)-propan-2-one (**2**). Several kinds of 1,2-benzenediol monoethers (**6a-k**) were also prepared from **3** using the corresponding alcohols. Pairs of the isomeric monomethyl ethers (**6d/6l**, and **6e/6n**) were synthesized regioselectively by this method. The present method is the first example of 1,2-benzenediol formation via the C3+C3 annulation.

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