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A New Entry to 1,2,4-Benzenetriol Congeners

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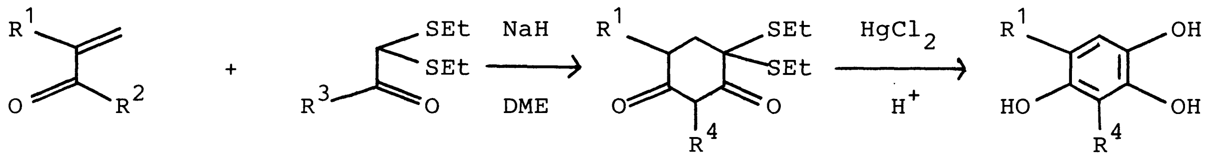
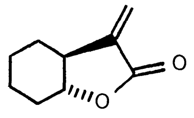
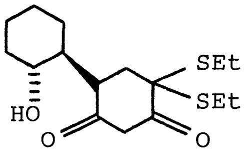
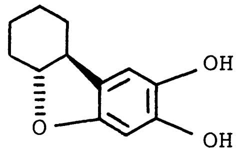
1,2,4-Benzenetriol derivatives were efficiently prepared from annulation of α,α-bis(ethylthio)carbonyl compounds with α,β-unsaturated carbonyl compounds.

The investigations on the annulation reactions leading to the substituted aromatic systems have been made extensively owing to several advantages.[1,2] To our knowledge, however, no successful attempt to form the 1,2,4-benzenetriol derivatives from aliphatic compounds has been reported. This oxygen arrangement on the aromatic ring is found widely in the structures of biologically active compounds and naturally occurring compounds such as oxydopamine, coumestans, pterocarpans, and rotenoids.[3] In general, 1,2,4-benzenetriols are obtained from Thiele reaction and reductive or oxidative reactions of appropriate cyclic compounds.[4] In connection with our synthetic studies[5] on aromatic compounds from aliphatic sources, we here describe a new regiocontrolled route to the title compounds **5** by the annulation reaction shown below.



1 **2 or 3** **4** **5**

Table 1. Preparation of cyclohexanediones and 1,2,4-benzenetriols

	1		2 or 3			4				5		
	R^1	R^2		R^3		R^1	R^4	yield/%		R^1	R^4	yield/%
a	H	Me	**2**	OMe	**a**	H	H	56	**a**	H	H	32
b	Me	Me	**2**	OMe	**b**	Me	H	91	**b**	Me	H	73
c	H	Et	**2**	OMe	**c**	H	Me	49	**c**	H	Me	64
d	Me	Et	**2**	OMe	**d**	Me	Me	46	**d**	Me	Me	75
e	H	OMe	**3**	Me	**a**	H	H	60				
f	Me	OMe	**3**	Me	**b**	Me	H	11				
 O **1g**			**3**	Me	 SEt SEt HO O O **4e**			78	 OH O OH **5e**			40

Preparation of the 1,2,4-benzenetriol derivatives **5** was achieved via the protected cyclohexanetriones (**4**) which were obtained from two type of the Michael reactions; one is the union of a two-carbon unit [methyl bis-(ethylthio)acetate (**2**)] with a four-carbon unit [the α,β-unsaturated ketone (**1a-d**)] and the other the union of two three-carbon units [1,1-bis(ethylthio)propan-2-one (**3**) and acrylate (**1e,f**)].

The reaction of α,β-unsaturated carbonyl compounds (**1**; 1.0 equiv.) with α,α-bis(ethylthio)carbonyl compound (**2**[6] or **3**; 1.0 equiv.) in the presence of sodium hydride (0.5-1.0 equiv.) in dimethoxyethane at room temperature gave 1,1-bis(ethylthio)-2,4-cyclohexanediones (**4**) by the MIRC (Michael Induced or Initiated Ring Closure) reaction.[2,7] Deprotection of **4** with mercuric chloride in aq. MeOH at room temperature gave a mixture of benzenetriol and carbonyl compounds which are considered to be tautomeric with triol. Heating of the mixture with acetic acid or formic acid under reflux for 1 h gave 1,2,4-benzenetriol (**5**) in moderate yields as shown in Table 1. As an application of the present method to a more complex molecule, the reaction of cyclic acrylate (**1g**) with **3** was carried out successfully to afford the benzofuran derivative (**5e**) via the intermediate (**4e**).

In summary, 1,2,4-benzenetriol derivatives (**5**) were constructed from 1,1-bis(ethylthio)-2,4-cyclohexanediones (**4**) which were readily derived from methyl bis(ethylthio)acetate (**2**) and 1,1-bis(ethylthio)propan-2-one (**3**). The present method is the first example of 1,2,4-benzenetriol formation via the Michael-type annulation of wide generality.

References

1) See, for example: G. H. Posner, S. Lu, E. Asirvatham, E. F. Silversmith, and E. M. Shulman, J. Am. Chem. Soc., 108, 511 (1986); H. Saimoto and T. Hiyama, Tetrahedron Lett., 27, 597 (1986); Y. Masuyama, H. Sato, and Y. Kurusu, ibid., 26, 67 (1985); D. L. Boger and M. D. Mullican, J. Org. Chem., 49, 4045 (1984); N. Takeuchi, N. Okada, and S. Tobinaga, Chem. Pharm. Bull., 31, 4355 (1983).

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3) J. L. Ingham, "Fortschritte der Chemie organishcher Naturstoffe," ed by W. Herz, H. Grisoebach, and G. W. Kirby, Springer-Verlag, Wien - New York (1983), Vol. 43, pp. 1-266.

4) J. Thiele, Ber., 31, 1247 (1898); J. Thiele and E. Winter, Justus Liebigs Ann. Chem., 311, 341 (1900); G. Pettersson, Acta Chem. Scand., 18, 1839 (1964); W. Flaig and J. Salfeld, Justus Liebigs Ann. Chem., 618, 117 (1958); R. Fittig and W. Siepermann, ibid., 180, 37 (1876); J. F. W. McOmie and J. M. Blatchly, Org. React., 19, 199 (1972).

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