A Convenient Synthesis of 2-Alkylated 1,4-Benzenediols

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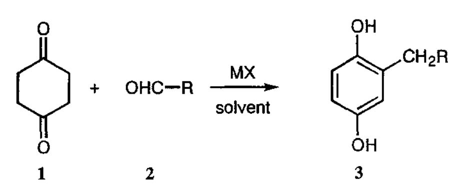
Abstract: Reaction of 1,4-cyclohexanedione with a variety of aldehydes in the presence of metal halides generated the 2-alkylated 1,4-benzenediols in good yields without any aromatic by-products.

The 1,4-benzenediol derivatives are found not only in the naturally occurring compounds[1] but also in the industrial products.[2] Some of the compounds are utilized extensively as the anti-oxidant chemicals,[3] photo-industry materials,[4] or polymer materials[5] owing to their own chemical properties. The variation of the substituents on the aromatic ring gives desired properties to the compounds themselves and their derivatives such as liquid-crystalline polyesters derived from the aromatic compounds.[5] In addition, many quinones derived from the aromatic compounds are used as dienophiles in the Diels-Alder reaction.[6] For these reasons, the supply of 1,4-benzenediols is significant in the synthetic organic chemistry. In general, the preparations of 2-alkylated 1,4-benzenediols employ the procedures starting from 1,4-benzenediol derivatives or 1,4-quinones followed by carbon-carbon bond formation reaction. The severe reaction condition has some limitation to the side chain structure on the aromatic rings synthesized. We disclose a new synthetic method for the 2-alkylated 1,4-benzenediols starting from 1,4-cyclohexanedione and a variety of aldehydes under non-acidic condition.

In the course of our study on the synthesis of aromatic compounds,[7] the 1,4-benzenediol formation was started from 1,4-cyclohexanedione (**1**). Reactions of the diketone (**1**) with aldehydes (**2**) were carried out in 1,3-dimethyl-2-imidazolidinone (DMI) in the presence of lithium chloride to give monoalkylated 1,4-benzenediols (**3**) as shown in Scheme 1. The isolated yields of 1,4-benzenediols (**3**) are shown in Tables 1-3. Other metal halides such as lithium bromide, lithium iodide, or magnesium chloride can be used instead of lithium chloride in the reactions as shown in Tables 1 and 3. Although the starting diketone (**2**) was detected in these crude products, no polyalkylated aromatic compounds nor structural isomers concerning the side chain on the aromatic ring were found. Inspection of these Tables indicates that lithium chloride was the best catalyst in those metal halides examined. The solvent, DMI can be replaced with other polar one such as HMPA, DMF, DMSO, 1,3-dimethyltetrahydro-2(1*H*)-pyrimidinone (DMPU),[8] 1,1,3,3-tetramethylurea (TMU), *N,N,N',N'*-tetramethylethylenediamime (TMEDA), or pyridine. Table 1 shows that DMI, HMPA, DMPU, and pyridine gave better yield in the reaction of benzaldehyde with **1**. Especially, pyridine is the most acceptable solvent when the aromatic aldehydes have an acidic substituent on their aromatic rings or in the case of aliphatic aldehyde as shown in Table 2 and 3.



Scheme 1

Table 1. Reactions of 1,4-cyclohexanedione with benzaldehyde

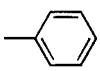
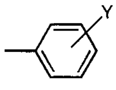
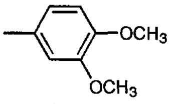
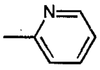
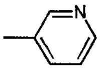
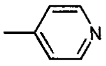
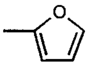
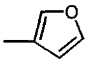
R	MX	Solvent	Yield (%)
	LiCl	DMI	85
	LiBr	DMI	72
	LiI	DMI	62
	$MgCl_2$	DMI	72
	LiCl	DMPU	76
	LiCl	DMSO	67
	LiCl	DMF	64
	LiCl	HMPA	80
	LiCl	TMU	75
	LiCl	Pyridine	76

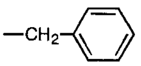
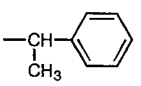
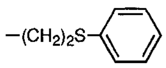
Table 2. Reactions of 1,4-cyclohexanedione with aromatic aldehydes

R	MX	Solvent	Yield (%)
 Y			
Y = 2-Cl	LiCl	DMI	86
Y = 3-Cl	LiCl	DMI	83
Y = 4-Cl	LiCl	DMI	85
Y = $4-NO_2$	LiCl	DMI	59
Y = 4-OH	LiCl	DMPU	37
Y = 4-OH	LiCl	Pyridine	63
Y = 4-OH	LiCl	TMEDA	78
Y = 4-COOH	LiCl	Pyridine	61
 OCH_3 OCH_3	LiCl	DMI	80
 N	LiCl	DMI	51
 N	LiCl	DMI	61
 N	LiCl	DMI	70
 O	LiCl	DMI	96
 O	LiCl	DMI	63

The conventional methods gave similar compounds by the Friedel-Crafts alkylation of 1,4-benzenediol derivatives, or by the reduction of aromatic ketones which were obtained from the Friedel-Crafts acylation reaction. The former method has a possibility to give polyalkylated aromatic compounds due to the higher reactivity of the monoalkylated aromatic ring. Further, the rearrangement reaction of an alkyl species can occur during the procedure and the resulting isomeric alkylated benzenediols can be obtained in some cases.[9] Therefore, it is anticipated that the 1,4-benzenediols listed in Table 3 are difficult to form by the Friedel-Crafts alkylation reaction because of the rearrangement. The latter acylation method has multi-steps and can offer only the compounds which are dull against both the acidic condition and the reductive one. The proposed synthetic method allows no side reaction in any instance as mentioned above. The first step of this procedure is the aldol condensation[10] between the ketone (**1**) and aldehydes (**2**). The intermediary α,β-unsaturated ketones have structures easy to isomerize to furnish the stable 1,4-benzenediols (**3**).

In conclusion, 1,4-cyclohexanedione was reacted with aldehydes to give 2-alkylated 1,4-benzenediols in the presence of metal halides in one-pot with simple operation. The procedure gave no aromatic by-products such as 1,4-benzenediols with isomerized side chain or polyalkylated 1,4-benzenediols.

Table 3. Reactions of 1,4-cyclohexanedione with aliphatic aldehydes

R	MX	Solvent	Yield (%)
	LiCl	DMI	81
	LiCl	DMI	74
	LiCl	DMI	54
$—(CH_2)_nCH_3$			
n = 1	LiCl	DMI	64
n = 4	LiCl	DMI	86
	LiCl	HMPA	80
n = 8	LiCl	DMI	52
	LiCl	Pyridine	83
	LiBr	Pyridine	63
	LiI	Pyridine	67
	$MgCl_2$	Pyridine	52
	$MgCl_2$	DMI	66
	$MgCl_2$	DMSO	56
n = 10	LiCl	Pyridine	65
n = 20	LiCl	Pyridine	52

Typical Procedure for the Reaction between 1 and 2 : A mixture of **1** (0.05 mol), **2** (0.05 mol), and metal halide (0.05 mol) in DMI (HMPA, DMF, DMSO, DMPU, or TMU) (20 ml) was heated on an oil bath with stirring at atomospheric pressure. The temperature of the bath was maintained at 160-170°C for 1 hr. When pyridine or TMEDA was used as the solvent, the reaction mixture was heated under reflux for 1 hr. The reaction mixture was poured into water and the product was extracted with ether. The organic extract was washed with brine, dried, and evaporated *in vacuo*. Purification of the residue was performed by column chromatography or recrystallization to give **3**.

References and Notes

(1) see for example: Cimino, G.; De Stefano, S.; Minale, L. *Tetrahedron* **1972**, *28*, 1315. Howard, B. M.; Clarkson, K.; *Tetrahedron Lett.* **1979**, 4449. Ochi, M.; Kotsuki, H.; Inoue, S.; Taniguchi, M.; Tokoroyama, T. *Chem. Lett.* **1979**, 831. Reynolds, G.; Rodriguez, E. *Phytochemistry* **1979**, *18*, 1567. Stonik, V. A.; Makarieva, T. N.; Dmitrenok, A. S. *J. Nat. Prod.* **1992**, *55*, 1256. De Rosa, S.; Crispino, A.; De Giulio, A.; Iodice, C.; Milone, A. *J. Nat. Prod.* **1995**, *58*, 1450. Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 1045.

(2) see for example: Asanuma, N.; Ooki, N.; Hirano, S. *Jpn. Kokai Tokkyo Koho* JP 06298688, 1994; *Chem. Abstr.* **1995**, *123*, 198414n. Many other patent aplications have been offered.

(3) Yamamura, T.; Nishiwaki, K.; Tanigaki, Y.; Terauchi, S.; Tomiyama, S; Nishiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2955.

(4) see for example: Sasaki, M.; Kato, K. *Jpn. Kokai Tokkyo Koho* JP 05313276, 1993; *Chem. Abstr.* **1995**, 121, 191105n. Hioki, T. *Jpn. Kokai Tokkyo Koho* JP 05313285, 1993; *Chem. Abstr.* **1995**, *121*, 191106p. Ooki, N.; Takahashi, O. *Jpn. Kokai Tokkyo Koho* JP 06161060, 1994; *Chem. Abstr.* **1995**, *121*, 267682w.

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(6) Butz, L. W.; Rytina, A. W. In *Organic Reactions*, Vol. 5; Adams, R., Ed.; Wiley: New York, **1949**; p 136.

(7) Ozaki, Y.; Imaizumi, K.; Okamura, K.; Morozumi, M.; Hosoya, A.; Kim, S. *Chem. Pharm. Bull.* **1996**, *44*, 1785 and references cited therein.

(8) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.

(9) Price, C. C. In *Organic Reactions*, Vol. 3; Adams, R., Ed.; Wiley: New York, **1946**, p 1. Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*, Vol 3; Trost, B. M., Ed., Pergamon: Oxford, **1991**, p 293.

(10) Aldol condensation reactions of alkyl ketones with enolisable and non-enolisable aldehydes using lithium iodide in ether, tetrahydrofuran, or benzene were reported. It was sugested that the condensations were promoted by a Li^+-complexed enols converted from ketones. Kellehter, R. G.; McKervey, M. A.; Vibuljan, P. *J. Chem. Soc., Chem. Commun.* **1980**, 486. The similar contribution of metal halides was expected in the reactions of 1,4-cyclohexanedione with aldehydes described above.