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Rapid synthesis of substituted 5-phenyl-1,3-dioxolan-4-ones under microwave-induced solvent-free conditions

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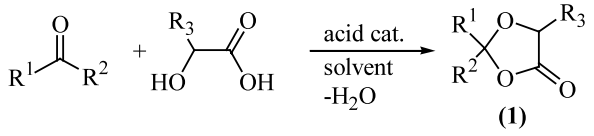
Abstract—Under microwave irradiation and without solvent, racemic and optically pure mandelic acid readily condenses with aldehydes and ketones to give 2-alkyl substituted 5-phenyl-1,3-dioxolan-4-ones in good yield.

In recent years, 1,3-dioxolan-4-ones (**1**) have served as precursors to a variety of synthetic targets. They have been used as substrates for the total synthesis of (*S*)-oxybutynin,[1] eicosanoids,[2] beta lactams,[3] a muscarinic receptor antagonist,[4] as well as in the synthesis of substituted tetrahydrofurans,[5] aldols and homoallylic alcohols,[6] chiral allylic[7] and chiral secondary alcohols.[8] Although other methods have been used,[9] 1,3-dioxolan-4-ones are most often prepared[10] by the acid or Lewis acid catalyzed condensation of an alpha hydroxy carboxylic acid with an aldehyde or ketone in an aromatic or hydrocarbon solvent (Eq. (1)).

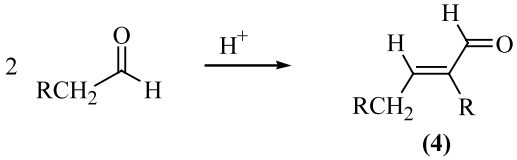


(1) (1)

Microwave-assisted organic synthesis has also received a great deal of recent attention[11] due to shorter reaction times, minimization of reaction byproducts, increased yields, and in many cases, solvent-free conditions. Many of these reactions have been supported on silica, alumina, clays, or resins. In this paper, we report the solvent free microwave-assisted synthesis of several alkyl substituted 5-phenyl-1,3-dioxolan-4-ones from mandelic acid and aldehydes or ketones using anhydrous copper sulfate as the support medium.

Our initial efforts employed the less expensive racemic mandelic acid as our starting α-hydroxy carboxylic acid and various aldehydes as the carbonyl component. Early attempts using silica, alumina, and k-10 montmorillonite as the solid support were disappointing and resulted in yields of 30% or less. However, upon changing to anhydrous copper sulfate, the yields dramatically improved into the 70–85% range as shown in Table 1. It is believed that the copper sulfate functions both as a Lewis acid catalyst and as a desiccant to remove the water that is generated in the condensation reaction.

As often occurs under microwave-induced conditions, the reaction products were formed with few impurities. The only byproduct observed was a small amount of the dehydrated aldol product (**4**, Eq. (2)) resulting from the acid-catalyzed self-condensation of the starting aldehyde. Ketones and aldehydes without α-hydrogens produced only the dioxolanone products. Whenever possible, the dioxolanones were formed as a *cis*/*trans* mixture of the 2,5-disubstituted or 2,2,5-trisubstituted ring products. Depending upon the aldehyde/ketone and the conditions used, the *cis*/*trans* ratios ranged from approximately 1:1 to 7:1 as determined by ^{1}H NMR. The *cis*/*trans* selectivity varied inversely with strength of the microwave radiation used. As observed in entries 1, 3, 5, 7, and 9 in Table 1, the *cis*/*trans* selectivity decreased as the microwave power increased. Fortunately, the major *cis*[12] dioxolanone product can be isolated in many cases by low temperature fractional crystallization or the *cis*/*trans* mixture can be readily separated by column chromatography.



(4) (2)

Keywords: microwave-induced; condensation; solvent-free conditions; dioxolane.

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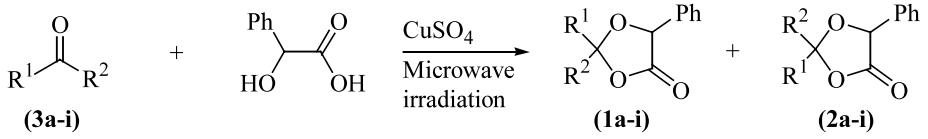
Unfortunately, every attempt to convert an aromatic or α,β-unsaturated aldehyde into a dioxolanone in an acceptable yield met with failure. Under current reaction conditions, it was impossible to obtain greater than 30% of the desired dioxolanone product. Attempts to add catalytic amounts of acid resulted in an ugly black mixture without an improved yield. Entries 17 and 18 in Table 1 show that the alkene functionality was not the cause; *Z*-4-heptenal reacted quite readily and gave excellent yields.

The dioxolanone derived from 4-methylcyclohexanone gave a 1:1 mixture of two diastereomers while the dioxolanone derived from racemic 2-methylcyclohexanone gave a mixture of four diastereomers; two major and two minor in an approximate 2:2:1:1 ratio as determined by proton NMR. The isolation and structural determination of these four diastereomers are currently under investigation.

In conclusion, we have shown that 2-alkyl and 2,2-dialkyl substituted 5-phenyl-1,3-dioxolan-4-ones can be readily synthesized from the corresponding aldehydes or ketones under microwave-assisted solvent-free conditions. This methodology not only reduces the necessary reaction time but also generates the products in a more environmentally friendly manner. We are continuing to investigate the optimization of this synthetic method and its application to the synthesis of dioxolanones generated from additional aldehydes and ketones as well as other α-hydroxy acids.

Table 1. Microwave-assisted solvent-free synthesis of 2-substituted 5-phenyl-1,3-dioxolan-4-ones



(3a-i) **(1a-i)** **(2a-i)**

a: R^1 = Butyl R^2 = H
b: R^1 = Pentyl R^2 = H
c: R^1 = Hexyl R^2 = H
d: R^1 = ^{t}Butyl R^2 = H
e: R^1 = z-3-Hexenyl R^2 = H
f: R^1 = ^{t}Butyl R^2 = Methyl
g: $R^1 = R^2 = -CH_2(CH_2)_3CH_2-$
h: $R^1 = R^2 = -(CH_2)_2CH(CH_3)(CH_2)_2-$
i: $R^1 = R^2 = -CH(CH_3)(CH_2)_4-$

Entry	Mand. acid[a]	Ald./ket.	Time[b] (min)	Power[c] (W)	Yield (%)[d]	*cis*/*trans*[e]
1	Racemic	**3a**	3 × 3	400	82	65:35
2	*S*-(+)	**3a**	3 × 3	400	78	65:35
3	Racemic	**3a**	3 × 3	300	82	77:23
4	*S*-(+)	**3a**	3 × 3	300	74	80:20
5	Racemic	**3a**	3 × 4	200	80	86:14
6	*S*-(+)	**3a**	3 × 4	200	68	85:15
7	Racemic	**3b**	3 × 3	400	81	65:35
8	*S*-(+)	**3b**	3 × 3	400	77	68:32
9	Racemic	**3b**	3 × 3	300	78	76:24
10	*S*-(+)	**3b**	3 × 3	300	71	82:18
11	Racemic	**3c**	3 × 3	400	77	69:31
12	*S*-(+)	**3c**	3 × 3	400	76	71:29
13	Racemic	**3c**	2 × 4	300	69	82:18
14	*S*-(+)	**3c**	3 × 3	300	61	88:12
15	Racemic	**3d**	2 × 4	300	61[f]	80:20
16	*S*-(+)	**3d**	2 × 4	300	23[f]	NA
17	Racemic	**3e**	3 × 3	400	91	74:26
18	*S*-(+)	**3e**	3 × 3	400	85	74:26
19	Racemic	**3f**	3 × 3	400	37	50:50
20	*S*-(+)	**3f**	3 × 3	400	35	50:50
21	Racemic	**3g**	3 × 3	400	83[f]	NA
22	*S*-(+)	**3g**	3 × 3	400	81[f]	NA
23	*S*-(+)	**3g**	3 × 3	300	73[f]	NA
24	Racemic	**3h**	3 × 3	400	86	2 enant. prs
25	*S*-(+)	**3h**	3 × 3	400	85	2 diast.
26	*S*-(+)	**3i**	3 × 3	400	69	4 diast.

[a] Reactions were run with either racemic or optically active mandelic acid as indicated.
[b] Number of irradiations for a given time; 2×4 indicates 2 irradiations of 4 min duration each.
[c] Domestic 1000 W microwave oven used at lesser power levels.
[d] Yields determined by ^{1}H NMR except where indicated.
[e] *cis*/*trans* ratios determined by ^{1}H NMR.
[f] Isolated yield.

Typical procedure[13]

Anhydrous copper sulfate (0.20 g, 1.3 mmol), mandelic acid (0.20 g, 1.3 mmol), and aldehyde or ketone (2.0 mmol, 1.5 equiv.) were placed in a 10×150 mm test tube. A rubber septum pierced by an open-ended capillary tube was loosely fitted into the mouth of the tube. The test tube (upright in a beaker) was placed into a domestic microwave oven and irradiated according to the data given in Table 1 with 1–2 min intervals between irradiations. **Caution**: the test tube and contents can become very hot! After cooling to room temperature, the mixture was dissolved in 3 mL of acetone, filtered through a short column of neutral alumina, and the column washed with an additional 4.0 mL of acetone. The solvent and volatiles were removed under vacuum, and the crude product was then purified by flash column chromatography (~5% ethyl acetate/hexane) if necessary.

Analytical data for new compounds

All new compounds given below were derived from (*S*)-(+)-mandelic acid.

(2*S*,5*S*)-2-Butyl-5-phenyl-1,3-dioxolan-4-one (**1a**): Anal. calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.25; H, 7.43. ^{1}H NMR ($CDCl_3$): δ 7.44–7.39 (m, 5H), 5.68 (t, J=4.8 Hz, 1H), 5.23 (s, 1H), 1.95 (dt, J=8.7, 4.9 Hz, 2H), 1.59–1.37 (m, 4H), 0.95 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.7, 133.6, 129.1, 128.7, 126.8, 104.5, 76.7, 33.7, 24.8, 22.3, 13.8.

(Mixture of 2*R*,5*S* and 2*S*,5*S*)-2-hexyl-5-phenyl-1,3-dioxolan-4-one: Anal. calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 71.28; H, 8.06. (2*S*,5*S cis*-**1c**): ^{1}H NMR ($CDCl_3$): δ 7.43–7.39 (m, 5H), 5.68 (t, J=4.7 Hz, 1H), 5.22 (s, 1H), 1.99–1.90 (m, 2H), 1.57–1.32 (m, 8H), 0.90 (t, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.7, 133.6, 129.1, 128.7, 126.8, 104.5, 76.7, 34.0, 31.5, 28.8, 22.7, 22.4, 14.0. (2*R*,5*S trans*-**2c**): ^{1}H NMR ($CDCl_3$): δ 7.44–7.38 (m, 5H), 5.78 (t, J=4.8 Hz, 1H), 5.38 (s, 1H), 1.98–1.85 (m, 2H), 1.59–1.30 (m, 8H), 0.89 (t, J=6.3 Hz, 3H).

(Mixture of 2*R*,5*S* and 2*S*,5*S*)-2-(*z*-3-hexenyl)-5-phenyl-1,3-dioxolan-4-one: Anal. calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.16; H, 7.51. (2*S*,5*S cis*-**1e**): ^{1}H NMR ($CDCl_3$): δ 7.44–7.36 (m, 5H), 5.70 (t, J=4.7 Hz, 1H), 5.41–5.20 (m, 2H) 5.13 (s, 1H), 2.20 (q, J=7.5 Hz, 2H), 2.02–1.85 (m, 4H), 0.87 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.6, 133.6, 133.4, 129.1, 128.7, 126.8, 126.5, 104.0, 76.7, 34.1, 20.7, 20.4, 14.2. (2*R*,5*S trans*-**2e**): ^{1}H NMR ($CDCl_3$): δ 7.47–7.35 (m, 5H), 5.78 (t, J=4.9 Hz, 1H), 5.50–5.26 (m, 2H), 5.40 (s, 1H).

(5*S*-**1h**): Mixture of two diastereomers: Anal. calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.17; H, 7.47. ^{1}H NMR ($CDCl_3$): δ 7.48–7.35 (m, 10 H), 5.40 (s, 1H), 5.36 (s, 1H), 2.09–1.74 (m, 12H), 1.51–1.32 (m, 6H), 0.96 (d, J=6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 171.4, 134.6, 128.8, 128.6, 126.32, 126.28, 111.7, 111.5, 75.43, 75.39, 36.4, 35.8, 35.6, 34.5, 31.4, 31.2, 31.1, 30.9, 30.6, 21.4, 21.2.

(5*S*-**1i**): Two minor diastereomers: Anal. calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.45; H, 7.38. ^{1}H NMR ($CDCl_3$): δ 7.50–7.34 (m, 10 H), 5.44 (s, 1H), 5.42 (s, 1H), 2.04–1.31 (m, 18H), 1.030 (d, J=6.7 Hz, 3H), 1.035 (d, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.7, 171.6, 135.5, 128.6, 126.8, 125.81, 125.77, 114.0, 113.7, 76.9, 76.5, 40.9, 40.1, 38.0, 37.0, 31.5, 31.0, 24.3, 24.1, 23.5, 22.9, 13.7. Two major diastereomers: Anal. calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.14; H, 7.58. ^{1}H NMR ($CDCl_3$): δ 7.49–7.38 (m, 10H), 5.39 (s, 1H), 5.33 (s, 1H), 2.20–1.20 (m, 18H), 1.05 (d, J=6.7 Hz, 3H), 1.01 (d, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.8, 171.7, 134.1, 133.9, 128.9, 128.6, 126.9, 126.8, 112.8, 112.7, 75.3, 75.0, 38.8, 38.6, 35.3, 34.3, 31.6, 30.7, 24.2, 24.1, 23.3, 23.2, 14.0, 13.8.

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